KAL 07-30-02

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=> b medline caplus lifesci embase uspatfull

COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'MEDLINE' ENTERED AT 15:55:15 ON 30 JUL 2002

FILE 'CAPLUS' ENTERED AT 15:55:15 ON 30 JUL 2002
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=> s p27kip1

L1         2711 P27KIP1

=> cyclin dependent kinase

CYCLIN IS NOT A RECOGNIZED COMMAND
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"HELP COMMANDS" at an arrow prompt (=>).

=> s l1 and cyclin dependent kinase

L2         2132 L1 AND CYCLIN DEPENDENT KINASE

=> s l2 (ear or hear?)

MISSING OPERATOR 'L12 (EAR'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l2 and (ear or hear?)

L3           46 L2 AND (EAR OR HEAR?)

=> dup rem l3

PROCESSING COMPLETED FOR L3
L4            37 DUP REM L3 (9 DUPLICATES REMOVED)

=> s l4 and py,1999

L5            0 L4 AND PY,1999

=> s l4 and py<1999

   3 FILES SEARCHED...
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L6 7 L4 AND PY<1999

=> d l6 ibib abs tot

L6 ANSWER 1 OF 7 MEDLINE
ACCESSION NUMBER: 1999106964 MEDLINE
DOCUMENT NUMBER: 99106964 PubMed ID: 9891946
TITLE: Cell cycle profiles and expressions of p21CIP1 AND **P27KIP1** during myocyte development.
AUTHOR: Poolman R A; Gilchrist R; Brooks G
CORPORATE SOURCE: Cardiovascular Cellular and Molecular Biology Laboratory, The Rayne Institute, St. Thomas' Hospital, London, United Kingdom.
SOURCE: INTERNATIONAL JOURNAL OF CARDIOLOGY, **(1998 Dec 1)** 67 (2) 133-42.
Journal code: 8200291. ISSN: 0167-5273.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990420
Last Updated on STN: 19990420
Entered Medline: 19990407

AB The ability of the cardiac myocyte to divide ceases shortly after birth. Thus, following severe injury, e.g., during myocardial infarction, the mature **heart** is unable to regenerate new tissue to replace the dead or damaged tissue. The identification of the molecules controlling the cessation of myocyte cell division may lead to therapeutic strategies which aim to re-populate the damaged myocardial area. Hence, we have determined the cell cycle profile, expressions and activities of the **cyclin-dependent kinase** inhibitors (CDKIs), p21CIP1 and **p27KIP1**, during rat ventricular myocyte development. Fluorescent activated cell sorting (FACS) analyses showed the percentage of S phase myocytes to be decreased significantly throughout development, concomitant with a significant increase in the percentage of G0/G1 and G2/M phase cells. The expression of p21CIP1 and **p27KIP1** increased significantly throughout cardiac development and complexed differentially with a number of cyclins and CDKs. Furthermore, an adult myocyte extract reduced neonatal myocyte CDK2 kinase activity significantly (>30%, p<0.05) whereas immunodepletion of p21CIP1 from adult lysates restored CDK2 kinase activity. Thus, p21CIP1 and **p27KIP1** may be important for the withdrawal of cardiac myocytes from the cell cycle and for maintaining the G0/G1 and G2/M phase blockades.

L6 ANSWER 2 OF 7 MEDLINE
ACCESSION NUMBER: 1998182413 MEDLINE
DOCUMENT NUMBER: 98182413 PubMed ID: 9515024
TITLE: Persistent and heterogenous expression of the **cyclin-dependent kinase** inhibitor, **p27KIP1**, in rat **hearts** during development.
AUTHOR: Koh K N; Kang M J; Frith-Terhune A; Park S K; Kim I; Lee C O; Koh G Y
CORPORATE SOURCE: Department of Physiology and Institute of Cardiovascular Research, Chonbuk National University Medical School, Chonju, 560-180, Republic of Korea.
SOURCE: JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY, **(1998 Mar)** 30 (3) 463-74.
Journal code: 0262322. ISSN: 0022-2828.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980514
Last Updated on STN: 19980514
Entered Medline: 19980501

AB We have previously shown that there were differential and dramatic decreases of cyclin and **cyclin-dependent kinase** (CDK) activities in cardiomyocytes during the neonatal period. The activity of CDKs control cell cycle progression, and this activity is regulated positively and negatively by association of CDKs with cyclins and **cyclin-dependent kinase** inhibitors (CKIs), respectively. While the INK family (p15(INK4B)/p16(INK4A)/p18(INK4C)/p19(INK4D)) of CKIs is not detectable in **hearts**, the KIP/CIP family (p21(CIP1), p27(KIP1) and p57(KIP2)) of CKIs is detectable in most organs including the **heart**. Differential and dramatic changes of the KIP/CIP family (p21(CIP1), p27(KIP1) and p57(KIP2)) of CKIs were detected in rat **hearts** during development. The mRNA and protein levels of p21(CIP1) and p57(KIP2) were readily detectable in **hearts** at gestational and early postnatal periods and decreased thereafter. The mRNA levels of p27(KIP1) in ventricles were high during the gestational period, and did not change until day 30 postnatal, then were decreased slightly in 90-day-old rats. The protein levels of p27(KIP1) increased significantly in the early postnatal period, then were expressed persistently, although levels decreased slightly in the adult period. However, protein levels of p27(KIP1) in atria did not change during development. Variable immuno-staining patterns of p27(KIP1) were observed at different periods of development and in various locations in myocardium. During the gestational period, approximately 35-50% of myocardial cells in the cardiac wall were p27(KIP1) immuno-positive and were distributed diffusely. These p27(KIP1) immunopositive cells increased predominantly in endocardial and mid-portion areas of ventricular myocardium at the early postnatal period. This heterogenous pattern of p27(KIP1) protein expression persisted to adult **hearts** though the percentage of p27(KIP1) immuno-positive cells decreased slightly. High magnification revealed that more than 50% of adult cardiomyocytes were p27(KIP1) immuno-positive and that p27(KIP1) was located solely in nuclei. These results indicate that p27(KIP1) may be an important inhibitor of CDK activities in cardiomyocytes during early postnatal development and may block the re-entrance of adult cardiomyocytes into the cell cycle after injury.

L6 ANSWER 3 OF 7 MEDLINE
ACCESSION NUMBER: 96189290 MEDLINE
DOCUMENT NUMBER: 96189290 PubMed ID: 8640801
TITLE: **Cyclin-dependent kinase** inhibitor p57KIP2 in soft tissue sarcomas and Wilms'tumors.
AUTHOR: Orlow I; Iavarone A; Crider-Miller S J; Bonilla F; Latres E; Lee M H; Gerald W L; Massague J; Weissman B E; Cordon-Cardo C
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York 10021, USA.
CONTRACT NUMBER: CA-47179 (NCI)
CA-47538 (NCI)
CA-DK-47650 (NCI)
+
SOURCE: CANCER RESEARCH, **(1996 Mar 15)** 56 (6) 1219-21.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607

ENTRY DATE: Entered STN: 19960726
Last Updated on STN: 20000303
Entered Medline: 19960715

AB Mammalian **cyclin-dependent kinase** inhibitors fall into two families, the INK4 and the CIP/KIP. The CIP/KIP family comprises three structurally related members, including p21CiP1/WAF1, **p27KIP1**, and p57KIP2. These proteins are all capable of inhibiting the progression of the cell cycle by binding and inhibiting G(1) cyclin/**cyclin-dependent kinase** complexes. In humans, p57KIP2 is expressed specifically in skeletal muscle, **heart**, brain, kidney, and lung. Human KIP2 resides in 11p15.5, a chromosomal region that is a common site for loss of heterozygosity in certain sarcomas, Wilms' tumors, and tumors associated with the Beckwith-Wiedemann syndrome. Because of the function, selective expression, and chromosomal location of p57KIP2, we undertook the present study to search for potential mutations of KIP2 in a cohort of 126 tumors composed of 75 soft tissue sarcomas and 51 Wilms' tumors. The KIP2 gene was characterized by Southern blot, comparative multiplex PCR, PCR -single-strand conformational polymorphism, and DNA sequencing assays in these neoplasms.
Deletions of the KIP2 gene or point mutations at the region encoding the **cyclin-dependent kinase** inhibitory domain were not found in the tumors analyzed. The absence of KIP2 mutations might indicate that these tumors arise due to defects at a closely linked but separate locus. Alternatively, similarly to the mouse homologue, inactivation of KIP2 could occur via genomic imprinting.

L6 ANSWER 4 OF 7 MEDLINE
ACCESSION NUMBER: 95247027 MEDLINE
DOCUMENT NUMBER: 95247027 PubMed ID: 7729683
TITLE: Cloning of p57KIP2, a **cyclin-dependent kinase** inhibitor with unique domain structure and tissue distribution.
AUTHOR: Lee M H; Reynisdottir I; Massague J
CORPORATE SOURCE: Cell Biology and Genetics Program, Howard Hughes Medical Institute, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
SOURCE: GENES AND DEVELOPMENT, **(1995 Mar 15)** 9 (6) 639-49.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U20553
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950608
Last Updated on STN: 19950608
Entered Medline: 19950601

AB Progression through the cell cycle is catalyzed by cyclin-dependent kinases (CDKs) and is negatively controlled by CDK inhibitors (CDIs). We have isolated a new member of the p21CIP1/**p27KIP1** CDI family and named it p57KIP2 to denote its apparent molecular mass and higher similarity to **p27KIP1**. Three distinct p57 cDNAs were cloned that differ at the start of their open reading frames and correspond to messages generated by the use of distinct splice acceptor sites. p57 is distinguished from p21 and p27 by its unique domain structure. Four distinct domains follow the heterogeneous amino-terminal region and include, in order, a p21/p27-related CDK inhibitory domain, a proline-rich (28% proline) domain, an acidic (36% glutamic or aspartic acid) domain, and a carboxy-terminal nuclear targeting domain that contains a putative CDK phosphorylation site and has sequence similarity to p27 but not to p21. Most of the acidic domain consists of a novel, tandemly repeated 4-amino acid motif. p57 is a potent inhibitor of G1- and S-phase CDKs

(cyclin E-cdk2, cyclin D2-cdk4, and cyclin A-cdk2) and, to lesser extent, of the mitotic cyclin B-Cdc2. In mammalian cells, p57 localizes to the nucleus, associates with G1 CDK components, and its overexpression causes a complete cell cycle arrest in G1 phase. In contrast to the widespread expression of p21 and p27 in human tissues, p57 is expressed in a tissue-specific manner, as a 1.5-kb species in placenta and at lower levels in various other tissues and a 7-kb mRNA species observed in skeletal muscle and **heart**. The expression pattern and unique domain structure of p57 suggest that this CDI may play a specialized role in cell cycle control.

L6 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:733410 CAPLUS
DOCUMENT NUMBER: 130:79180
TITLE: Expressions and activities of cell cycle regulatory molecules during the transition from myocyte hyperplasia to hypertrophy
AUTHOR(S): Poolman, Robert A.; Brooks, Gavin
CORPORATE SOURCE: Cardiovascular Cellular and Molecular Biology, The Rayne Institute, St Thomas' Hospital, London, SE1 7EH, UK
SOURCE: Journal of Molecular and Cellular Cardiology (**1998**), 30(10), 2121-2135
CODEN: JMCDAY; ISSN: 0022-2828
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of cell cycle dependent mols. in controlling the switch from cardiac myocyte hyperplasia to hypertrophy remains unclear, although in the rat this process occurs between day 3 and 4 after birth. In this study we have detd. (1) cell cycle profiles by fluorescence activated cell sorting (FACS); and (2) expressions, co-expressions and activities of a no. of cyclins, cyclin-dependent kinases (CDKs) and CDK inhibitors by reverse transcriptase polymerase chain reaction (RT-PCR), immunoblotting and in vitro kinase assays in freshly isolated rat cardiac myocytes obtained from 2, 3, 4 and 5-day-old animals. The percentage of myocytes found in the S phase of the cell cycle decreased significantly during the transition from hyperplasia to hypertrophy (5.5, 3.5, 2.3 and 1.9% of cells in 2-, 3-, 4- and 5-day-old myocytes, resp., $P<0.05$), concomitant with a significant increase in the percentage of G0/G1 phase cells. At the mol. level, the expressions and activities of G1/S and G2/M phase acting cyclins and CDKs were downregulated significantly during the transition from hyperplasia to hypertrophy, whereas the expressions and activities of G1 phase acting cyclins and CDKs were upregulated significantly during this transition. In addn., p21CIP1 -and **p27KIP1** -assocd. CDK kinase activities remained relatively const. when histone H1 was used as a substrate, whereas phosphorylation of the retinoblastoma protein was upregulated significantly during the transition from hyperplasia to hypertrophy. Thus, there is a progressive and significant G0/G1 phase blockade during the transition from myocyte hyperplasia to hypertrophy. While CDK2 and cdc2 may be pivotal in the withdrawal of cardiac myocytes from the cell cycle, CDK4 and CDK6 may be crit. for maintaining hypertrophic growth of the myocyte during development. (c) 1998 Academic Press.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:633529 CAPLUS
DOCUMENT NUMBER: 127:317518
TITLE: Downregulation of **cyclin-dependent**

kinase inhibitors p21 and p27 in pressure-overload hypertrophy

AUTHOR(S): Li, Jian-Mei; Brooks, Gavin

CORPORATE SOURCE: Cardiovascular Cellular and Mol. Biol., Cardiovascular Res., St. Thomas' Hosp., Rayne Inst., London, SE1 7EH, UK

SOURCE: American Journal of Physiology (**1997**), 273(3, Pt. 2), H1358-H1367
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors postulated that the **cyclin-dependent kinase** inhibitors p21 and p27 could regulate the alterations in growth potential of cardiomyocytes during left ventricular hypertrophy (LVH). LVH was induced in adult rat **hearts** by aortic constriction (AC) and was monitored at days 0, 1, 3, 7, 14, 21, and 42 postoperation. Relative to sham-operated controls (SH), left ventricle (LV) wt.-to-body wt. ratio in AC increased progressively with time without significant differences in body wt. or right ventricle wt.-to-body wt. ratio. Atrial natriuretic factor mRNA increased significantly in AC to 287% at day 42 compared with SH, whereas p21 and p27 mRNA expression in AC rats decreased significantly by 58% and 40% at day 7, resp. P21 and p27 protein expression decreased significantly from days 3 to 21 in AC vs. SH, concomitant with LV adaptive growth. Immunocytochem. showed p21 and p27 expression in cardiomyocyte nuclei. Thus downregulation of p21 and p27 may modulate the adaptive growth of cardiomyocytes during pressure overload-induced LVH.

L6 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:501917 CAPLUS

DOCUMENT NUMBER: 123:189996

TITLE: p57KIP2, a structurally distinct member of the p21CIP1 Cdk inhibitor family, is a candidate tumor suppressor gene

AUTHOR(S): Matsuoka, Shuhei; Edwards, Michael C.; Bai, Chang; Parker, Susan; Zhang, Pumin; Baldini, Antonio; Harper, J. Wade; Elledge, Stephen J.

CORPORATE SOURCE: Howard Hughes Medical Inst., Baylor College of Medicine, Houston, TX, 77030, USA

SOURCE: Genes Dev. (**1995**), 9(6), 650-62
CODEN: GEDEEP; ISSN: 0890-9369

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cyclin-dependent kinases (Cdks) are pos. regulators of cell proliferation whereas Cdk inhibitors (CKIs) inhibit proliferation. We describe a new CKI, p57KIP2, which is related to p21CIP1 and **p27KIP1**. Protein p57KIP2 is a potent, tight-binding inhibitor of several G1 cyclin/Cdk complexes, and its binding is cyclin dependent. Unlike CIP1, KIP2 is not regulated by p53. Overexpression of p57KIP2 arrests cells in G1. P57KIP2 proteins have a complex structure. Mouse p57KIP2 consists of four structurally distinct domains: an amino-terminal Cdk inhibitory domain, a proline-rich domain, an acidic-repeat region, and a carboxy-terminal domain conserved with **p27KIP1**. Human p57KIP2 appears to have conserved the amino- and carboxy-terminal domains but has replaced the internal regions with sequences contg. proline-alanine repeats. In situ hybridization during mouse embryogenesis revealed that KIP2 mRNA displays a striking pattern of expression during development, showing high level

expression in skeletal muscle, brain, **heart**, lungs, and eye.
Most of the KIP2-expressing cells are terminally differentiated, suggesting that p57KIP2 is involved in decisions to exit the cell cycle during development and differentiation. Human KIP2 is located at 11p15.5,
a region implicated in both sporadic cancers and Beckwith-Wiedemann syndrome, a familial cancer syndrome, marking it as a candidate tumor suppressor. The discovery of a new member of the p21CIP1 inhibitor family
with novel structural features and expression patterns suggests a complex role for these proteins in cell cycle control and development.

=> d history

(FILE 'HOME' ENTERED AT 15:55:03 ON 30 JUL 2002)

FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL' ENTERED AT 15:55:15 ON
30 JUL 2002
L1 2711 S P27KIP1
L2 2132 S L1 AND CYCLIN DEPENDENT KINASE
L3 46 S L2 AND (EAR OR HEAR?)
L4 37 DUP REM L3 (9 DUPLICATES REMOVED)
L5 0 S L4 AND PY,1999
L6 7 S L4 AND PY<1999

=> s l2 and (antisens? or ribozym?)

L7 149 L2 AND (ANTISENS? OR RIBOZYM?)

=> dup rem l7

PROCESSING COMPLETED FOR L7
L8 122 DUP REM L7 (27 DUPLICATES REMOVED)

=> s l8 and py<1999

3 FILES SEARCHED...
L9 33 L8 AND PY<1999

=> d l9 ibib abs tot

L9 ANSWER 1 OF 33 MEDLINE
ACCESSION NUMBER: 1999074700 MEDLINE
DOCUMENT NUMBER: 99074700 PubMed ID: 9857383
TITLE: Angiotensin II is involved in the progression of renal disease: importance of non-hemodynamic mechanisms.
AUTHOR: Wolf G
CORPORATE SOURCE: Department of Medicine, University of Hamburg, Germany.. WOLF@UKE.uni-hamburg.de
SOURCE: NEPHROLOGIE, **(1998)** 19 (7) 451-6. Ref: 51
Journal code: 8011169. ISSN: 0250-4960.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19990107
AB Several recent studies have provided clear evidence that

angiotensin-converting enzyme (ACE)-inhibitors slow the progression of renal disease. These effects are mainly independent from a comitant reduction in systemic blood pressure. Thus, angiotensin II (Ang II) exerts other effects on the kidney which are involved in the loss of renal function. Ang II induces proliferation of cultured mesangial and glomerular endothelial cells. Our group was the first to demonstrate that Ang II stimulates hypertrophy of cultured proximal tubular cells. Ang II stimulates bioactivation and expression of transforming growth factor-beta (TGF-beta) in tubular MCT cells. This Ang II-mediated expression of TGF-beta is due to an increase in transcriptional activity. A neutralizing anti-TGF-beta antibody attenuates the Ang II-induced increase in protein synthesis in MCT cells suggesting that the hypertrophy is mediated by synthesis and activation of endogenous TGF-beta. Proximal tubular cells undergoing Ang II-mediated hypertrophy are arrested in the G1-phase of the cell cycle and express typical G1-phase-associated genes. Induction of such G1-phase-associated early growth response genes have been also described in vivo after infusion of Ang II into the renal artery. This G1-phase arrest depends on the induction of the **cyclin-dependent kinase** (CdK) inhibitor **p27Kip1**. **p27Kip1** expression is stimulated after incubation of LLC-PK1 cells with Ang II or TGF-beta and binds to cyclin D1-CdK4 complexes, inhibits their kinase activity, and hampers G1-phase exit. Ang II stimulates transcription of collagen type IV in MCT cells. In addition to the classical a1 (IV) chain, a3 (IV) collagen, which has normally a restricted localization in the kidney, is also induced. This stimulation is mediated by endogenous synthesis and autocrine action of TGF-beta because a neutralizing anti-TGF-beta antibody as well as TGF-beta **antisense** oligonucleotides attenuate Ang II-induced collagen type IV transcription and synthesis. In addition, Ang II exerts immunomodulatory effects on the kidney through the induction of chemokines such as MCP-1 and RANTES. In conclusion, Ang II has emerged as a multifunctional acting as a growth factor and a profibrogenic cytokine, and even having inflammatory properties.

L9 ANSWER 2 OF 33 MEDLINE
ACCESSION NUMBER: 1999070369 MEDLINE
DOCUMENT NUMBER: 99070369 PubMed ID: 9853257
TITLE: Angiotensin II-mediated expression of **p27Kip1** and induction of cellular hypertrophy in renal tubular cells depend on the generation of oxygen radicals.
COMMENT: Comment in: Kidney Int. 1998 Dec;54(6):2241-2
AUTHOR: Hannken T; Schroeder R; Stahl R A; Wolf G
CORPORATE SOURCE: Department of Medicine, University of Hamburg, Germany.
SOURCE: KIDNEY INTERNATIONAL, **(1998 Dec)** 54 (6) 1923-33.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990211

AB BACKGROUND: Angiotensin II (Ang II) induces hypertrophy of cultured proximal tubular cells. We have previously demonstrated that this Ang II-mediated hypertrophy occurs in the G1-phase of the cell cycle and depends on the induction of **p27Kip1**, an inhibitor of G1-phase cyclin/**cyclin-dependent kinase** complexes.
The present study was undertaken to investigate whether Ang II may stimulate superoxide anions (O2.) formation in cultured LLC-PK1 and cultured mouse proximal tubule (MCT) cells, and to gain further insight

into a potential relationship between O2. and cell cycle regulation. METHODS: Reactive oxygen species were measured with the lucigenin method in intact cells. The effects of various inhibitors were tested on Ang II-induced O2. production. Cells were transiently transfected with phosphorothioate-modified rat p22phox **antisense** oligonucleotides to investigate the potential role of NAD(P)H oxidase. Expression of p22phox mRNA after Ang II-treatment was detected with Northern blots. Incorporation of [3H]leucine into de novo synthesized proteins was used as a parameter of cell hypertrophy. Expression of **p27Kip1** was evaluated in cell lysates by Western blotting. RESULTS: Ang II stimulated the accumulation of O2. in tubular cells; however, an addition of two different antioxidants completely abolished measurable O2. This effect was transduced by angiotensin receptor type-1 (AT1) and was inhibited by a flavoprotein inhibitor (DIP) or p22phox **antisense** oligonucleotides, indicating the involvement of membrane NAD(P)H oxidase. Ang II-stimulated de novo protein synthesis was attenuated by DIP, antioxidants, and p22phox **antisense** oligonucleotides. The Ang II-induced expression of **p27Kip1** protein and cellular hypertrophy were reduced by similar treatments. Generation of O2. by xanthine supplementation also stimulated **p27Kip1** expression and induced hypertrophy in LLC-PK1 cells. CONCLUSIONS: This study provides the first evidence, to our knowledge, that Ang II induces O2. in cultured tubular cells. Ang II-mediated activation of membrane bound NAD(P)H oxidase, probably by an increase in p22phox transcripts, is likely responsible for this induction. Generation of O2. subsequently induces **p27Kip1** expression and stimulates hypertrophy, suggesting a novel mechanism of how Ang II can modulate cell cycle regulation.

L9 ANSWER 3 OF 33 MEDLINE

ACCESSION NUMBER: 1999063523 MEDLINE
DOCUMENT NUMBER: 99063523 PubMed ID: 9848777
TITLE: Lovastatin inhibits mesangial cell proliferation via **p27Kip1**.
AUTHOR: Terada Y; Inoshita S; Nakashima O; Yamada T; Kuwahara M; Sasaki S; Marumo F
CORPORATE SOURCE: Second Department of Internal Medicine, Tokyo Medical and Dental University, Japan.
SOURCE: JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, **(1998 Dec)** 9 (12) 2235-43.
Journal code: 9013836. ISSN: 1046-6673.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990504
Last Updated on STN: 19990504
Entered Medline: 19990419

AB Mesangial cell proliferation is a key feature of glomerulonephritis. The hydroxymethylglutaryl-coenzyme A reductase inhibitor lovastatin is known to inhibit cell cycle progression. To determine the inhibitory mechanisms of mesangial cell proliferation by lovastatin, the **cyclin-dependent kinase** (CDK) activity, and expression of CDK inhibitor (**p27Kip1**, p21Cip1, and p16INK4) mRNA and protein were measured. Lovastatin inhibited phosphorylation of retinoblastoma protein and mesangial cell proliferation dose dependently. Lovastatin increased the **p27Kip1** protein level but produced no changes in the abundance of the **p27Kip1** mRNA level both in the presence and absence of mitogens. Treatment with lovastatin revealed the increment of both CDK2- and CDK4-bound-**p27Kip1**. The experiment using **antisense** oligonucleotide against **p27Kip1** showed significant amelioration of lovastatin-induced cell cycle arrest. Lovastatin reduced both platelet-derived growth factor-stimulated CDK2 and

CDK4 kinase activities. In conclusion, lovastatin inhibited mesangial proliferation via translational upregulation or impairment of **p27Kip1** protein degradation. Lovastatin serves as a potential therapeutic approach to mesangial proliferative disease.

L9 ANSWER 4 OF 33 MEDLINE
ACCESSION NUMBER: 1998361346 MEDLINE
DOCUMENT NUMBER: 98361346 PubMed ID: 9697881
TITLE: Lowering of **p27Kip1** levels by its **antisense** or by development of resistance to 1,25-dihydroxyvitamin D3 reverses the G1 block but not differentiation of HL60 cells.
AUTHOR: Wang Q M; Chen F; Luo X; Moore D C; Flanagan M; Studzinski G P
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, UMD - New Jersey Medical School, Newark 07103, USA.
CONTRACT NUMBER: RO1-CA 44722 (NCI)
SOURCE: LEUKEMIA, **(1998 Aug)** 12 (8) 1256-65.
Journal code: 8704895. ISSN: 0887-6924.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980828
Last Updated on STN: 19980828
Entered Medline: 19980819

AB **Cyclin-dependent kinase** inhibitors are proteins with functions which appear to involve regulation of cell cycle traverse, and have been suggested to have a role in cell differentiation. However, there is as yet no rigorous proof that this is the case. We have addressed the participation of one of these inhibitors, **p27Kip1**, in the induction of differentiation and the subsequent G1 block induced in HL60 cells by 1,25-dihydroxyvitamin D3 (1,25D3). First, it was noted that sublines of HL60 cells able to grow rapidly in the presence of 1,25D3 have protein levels of **p27Kip1** lower than the levels in cells subjected to 1,25D3-induced growth inhibition, but higher than in untreated parental cells. In contrast, there was no discernible relationship between the levels of **p27Kip1** and the expression of differentiation markers. Further, HL60 cells treated with 1,25D3 and an oligonucleotide **antisense**, but not mismatched, to **p27Kip1** showed an almost complete elimination of the 1,25D3-induced G1 block, but no decrease in the expression of differentiation markers. Similar results were obtained following transient transfection with an expression vector bearing the entire **p27Kip1** coding sequence in the anti-sense orientation. This is the first direct demonstration that **p27Kip1** plays a role in the 1,25D3-induced G1 arrest, and that partial reduction in its levels has no effect on the induction of differentiation in HL60 cells.

L9 ANSWER 5 OF 33 MEDLINE
ACCESSION NUMBER: 1998212757 MEDLINE
DOCUMENT NUMBER: 98212757 PubMed ID: 9551393
TITLE: Glomerular expression of **p27Kip1** in diabetic db/db mouse: role of hyperglycemia.
AUTHOR: Wolf G; Schroeder R; Thaiss F; Ziyadeh F N; Helmchen U; Stahl R A
CORPORATE SOURCE: Department of Medicine, University of Hamburg, Germany.. WOLF@UKE.uni-hamburg.de
SOURCE: KIDNEY INTERNATIONAL, **(1998 Apr)** 53 (4) 869-79.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980522

AB Early diabetic nephropathy is characterized by glomerular hypertrophy. Previous studies in vitro have demonstrated that mesangial cells exposed to high glucose are arrested in the G1-phase of the cell cycle and express increased levels of the **cyclin-dependent kinase** inhibitor **p27Kip1**. The present study was performed to investigate the renal expression of **p27Kip1** in db/db mice, a model of diabetes mellitus type II. Glomerular **p27Kip1** protein, but not mRNA expression, was strongly enhanced in diabetic db/db mice compared with non-diabetic db/+ littermates. Immunohistochemical studies revealed that this stimulated expression was mainly restricted to the nuclei of mesangial cells and podocytes, but glomerular endothelial cells occasionally also stained positively. Quantification of **p27Kip1** positive glomerular cells showed a significant increase of these cells in db/db mice compared with non-diabetic db/+ animals. Although tubular cells revealed a positive staining for **p27Kip1** protein, there was no difference between db/+ and db/db mice. Immunoprecipitation experiments revealed that **p27Kip1** protein associates with Cdk2 and Cdk4, but not with Cdk6. To test for the influence of hyperglycemia on cell cycle arrest and **p27Kip1** expression, mesangial cells were isolated from db/+ and db/db mice. There was a similar basal proliferation when these cells were grown in normal glucose-containing medium (100 mg/dl). However, raising the glucose concentration to 275 to 450 mg/dl induced cell cycle arrest in db/+ as well as db/db mesangial cells. Increasing the medium osmolarity with D-mannitol failed to induce **p27Kip1** expression in mesangial cells. Transfection of cells with **p27Kip1 antisense**, but not missense, phosphorothioate oligonucleotides facilitated cell cycle progression equally well in db/+ and db/db mesangial cells. Furthermore, **p27Kip1** expression was comparable in both cell lines in normal glucose, but increased in high glucose medium. Our studies demonstrate that **p27Kip1** expression is enhanced in diabetic db/db animals. This induction appears to be due to hyperglycemia. Expression of **p27Kip1** may be important in cell cycle arrest and hypertrophy of mesangial cells during early diabetic nephropathy.

L9 ANSWER 6 OF 33 MEDLINE
ACCESSION NUMBER: 1998147363 MEDLINE
DOCUMENT NUMBER: 98147363 PubMed ID: 9488039
TITLE: Identification of cdk2 binding sites on the **p27Kip1 cyclin-dependent kinase** inhibitor.
AUTHOR: Kwon T K; Nordin A A
CORPORATE SOURCE: Laboratory of Immunology, Gerontology Research Center, National Institute on Aging, NIH, Baltimore, Maryland 21224, USA.
SOURCE: ONCOGENE, **(1998 Feb 12)** 16 (6) 755-62.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980326
Last Updated on STN: 19980326
Entered Medline: 19980313

AB A cdk2 binding domain on **p27Kip1** located within the sequence of amino acids 53-85 was further characterized by generating a series of

point mutations within amino acid residues 62-75. Two regions, FDF (residues 62-64) and GXY (residues 72 and 74), were identified within the beta hairpin region of **p27Kip1**. Mutations within these regions essentially completely inhibited the binding to in vitro translated cdk2 and cdk2/cyclin E complexes formed in vitro or in vivo. The **p27Kip1** GST-fusion protein of the point mutation that replaces phenylalanine at residue 64 to alanine (F64A) showed approximately twofold less inhibition of cdk2 kinase activity. The cellular response to the introduction of the F64A mutant form of **p27Kip1** was compared to that of **p27Kip1** wild type by transfecting HeLa cells with constructs of full length sense and **antisense** coding sequences. Overexpression of the F64A mutant form of **p27Kip1** bound significantly lower levels of cdk2 as compared to wild type and did not affect the cdk2 related kinase activity of the transfected HeLa cells. Overexpression of wild type **p27Kip1** resulted in a reduction of the level of cdk2 kinase activity and effectively suppressed the growth of the transfected HeLa cells.

L9 ANSWER 7 OF 33 MEDLINE
ACCESSION NUMBER: 1998074641 MEDLINE
DOCUMENT NUMBER: 98074641 PubMed ID: 9413161
TITLE: Effect of dibutyryl cyclic AMP on the **cyclin-dependent kinase** inhibitor **p27Kip1** in the human hepatoma cells PLC/PRF/5.
AUTHOR: Kikukawa M; Okamoto Y; Fukui H; Nakano H
CORPORATE SOURCE: Third Department of Internal Medicine, Nara Medical University, Japan.
SOURCE: ANTICANCER RESEARCH, **(1997 Sep-Oct)** 17 (5A) 3287-91.
Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980130
Last Updated on STN: 19980130
Entered Medline: 19980120

AB The **cyclin-dependent kinase** (cdk) inhibitor **p27Kip1** is known to play a role in cell-cycle regulation at G1 and G1/S phase. We investigated the effect of the putative growth-inhibiting agent dibutyryl cyclic AMP (DBcAMP) on the serial changes of **p27Kip1** expression in the human hepatoma cells PLC/PRF/5 in culture. The **p27Kip1** protein level increased at an early stage of G1 phase (2 hours) after a release from serum-starvation and subsequently maintained the level until the entry to S phase, whereas an addition of DBcAMP at 1mM increased the **p27Kip1** protein level during G1 phase. In contrast, the relative expression levels of **p27Kip1** mRNA at 2 hours, 4 hours and 6 hours were lower in DBcAMP-added cells. The effects of DBcAMP on cell growth were, reduction of S-phase cells, inhibition of DNA synthesis, and accumulation of G2-phase cells. In the presence of the **antisense** oligodeoxynucleotides against **p27Kip1** mRNA, DBcAMP-induced growth inhibition was partially abolished. These findings suggest that DBcAMP elevates **p27Kip1** protein expression during G1 phase, which could be associated with growth inhibition. DBcAMP may inhibit the degradation of **p27Kip1** protein.

L9 ANSWER 8 OF 33 MEDLINE
ACCESSION NUMBER: 97361638 MEDLINE
DOCUMENT NUMBER: 97361638 PubMed ID: 9218599
TITLE: The CDK inhibitor, **p27Kip1**, is required for IL-4 regulation of astrocyte proliferation.
AUTHOR: Liu J; Flanagan W M; Drazba J A; Estes M L; Barnett G H;

Haqqi T; Kondo S; Barna B P
CORPORATE SOURCE: Department of Neurological Surgery, The Cleveland Clinic Foundation, OH 44195, USA.
CONTRACT NUMBER: RO1NS-33932 (NINDS)
SOURCE: JOURNAL OF IMMUNOLOGY, **(1997 Jul 15)** 159 (2) 812-9.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970813
Last Updated on STN: 19980206
Entered Medline: 19970805

AB IL-4 is a pleiotrophic cytokine that has been shown to affect cells of the central nervous system. We have demonstrated that IL-4 inhibits DNA synthesis and proliferation in human astroglia expressing IL-4 receptors. In this study, we sought to identify mechanisms that could account for the antimitogenic effects of IL-4. Epidermal growth factor (EGF)-stimulated human astroglia were arrested in G1 phase by IL-4, even though IL-4 stimulated levels of the G1 cyclins, D1 and E. Histone H1 kinase activity of cdk2 immunoprecipitates, however, was sharply reduced by IL-4; impairment of kinase activity was also evident in cyclin E immunoprecipitates, which contained evidence of hypophosphorylated (inactive) cdk2 product. Reduced cyclin E-associated cdk2 activity was not due to impaired **cyclin-dependent kinase** -activating kinase (CAK) activity, which was unaffected by IL-4. Inactive cyclin E/cdk2 complexes from IL-4 + EGF-treated cells contained, however, strikingly elevated **p27Kip1** cdk inhibitor. Elevated p27 was also detectable in whole cell lysates after 24 and 48 h of IL-4 treatment; by 72 h, p27 was no longer elevated. Pretreatment with **antisense** but not mismatch p27 oligonucleotides attenuated the inhibitory effects of IL-4 on DNA synthesis and histone kinase activity of cyclin E/cdk2 complexes. **Antisense** p27 also abrogated IL-4-mediated elevation of p27 in whole cell lysates and cyclin E/cdk2 complexes. These findings demonstrate that IL-4 regulates the cell cycle machinery of astroglial cells via a **p27Kip1** braking mechanism.

L9 ANSWER 9 OF 33 MEDLINE
ACCESSION NUMBER: 97262047 MEDLINE
DOCUMENT NUMBER: 97262047 PubMed ID: 9108461
TITLE: **Antisense** to cyclin D1 inhibits the growth and tumorigenicity of human colon cancer cells.
AUTHOR: Arber N; Doki Y; Han E K; Sgambato A; Zhou P; Kim N H; Delohery T; Klein M G; Holt P R; Weinstein I B
CORPORATE SOURCE: Herbert Irving Comprehensive Cancer Center, College of Physicians and Surgeons, Columbia University, New York, New York 10032, USA.
CONTRACT NUMBER: RO1-63467
SOURCE: CANCER RESEARCH, **(1997 Apr 15)** 57 (8) 1569-74.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970507
Last Updated on STN: 20000303
Entered Medline: 19970501

AB Cyclin D1 plays an important role in regulating the progression of cells

through the G1 phase of the cell cycle. This gene is frequently overexpressed in human colon cancer. To address the role of cyclin D1 in growth control and tumorigenesis in this disease, we have overexpressed an **antisense** cyclin D1 cDNA construct in the human colon cancer cell line SW480E8, which expresses high levels of cyclin D1. The integration and expression of the **antisense** construct was verified by Southern and Northern blot analyses, respectively, and resulted in decreased expression of the cyclin D1 protein. This was associated with decreased levels of the Rb and **p27Kip1** proteins. In addition, the hypophosphorylated form of Rb was increased in these cells. The SW480E8 **antisense** cyclin D1 cells displayed an increased doubling time, a decrease in saturation density, decreased plating efficiency and anchorage-independent growth, and a loss of tumorigenicity in nude mice. These findings provide direct evidence that increased expression of cyclin D1 in colon tumor cells contributes to their abnormal growth and tumorigenicity. The ability to revert the transformed phenotype of these cells with **antisense** cyclin D1 suggests that cyclin D1 or its associated **cyclin-dependent kinase** 4 may be useful targets in the therapy of colon cancer.

L9 ANSWER 10 OF 33 MEDLINE
ACCESSION NUMBER: 97193351 MEDLINE
DOCUMENT NUMBER: 97193351 PubMed ID: 9040942
TITLE: The role of **p27kip1** in the in vitro differentiation of murine keratinocytes.
AUTHOR: Hauser P J; Agrawal D; Flanagan M; Pledger W J
CORPORATE SOURCE: Department of Cell Biology, Vanderbilt University, Nashville, Tennessee 37240, USA.
CONTRACT NUMBER: CA67360 (NCI)
SOURCE: CELL GROWTH AND DIFFERENTIATION, **(1997 Feb)** 8 (2) 203-11.
Journal code: 9100024. ISSN: 1044-9523.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970514
Last Updated on STN: 19970514
Entered Medline: 19970506

AB We have studied the regulation of cyclins and **cyclin-dependent kinase** activities during differentiation of primary mouse keratinocytes. Differentiation was induced by placing primary murine keratinocytes into suspension culture, under conditions which prevent cells from attaching to any surface. This treatment induces synthesis of keratin 1, one of the earliest known markers of keratinocyte differentiation, and also results in a profound change in the regulation of G1 and S-phase cyclins and their associated proteins as well as their activities. The placement of cells in suspension culture reduced cyclin A, D1, and E kinase activity within 6 h, accompanied by the cessation of DNA synthesis. K1 mRNA levels were observed to increase after this period, supporting the hypothesis that cell cycle withdrawal precedes the differentiation program. Our data further revealed that the **p27kip1** protein level and associated **cyclin-dependent kinase** inhibitory activity increased when keratinocytes were induced to differentiate. Pretreatment of adherent keratinocytes with **p27kip1 antisense** oligonucleotides dramatically reduced the accumulation of **p27kip1** protein upon subsequent suspension culturing and prevented the onset of differentiation independently of the loss of **cyclin-dependent kinase** activities. Although **antisense** oligonucleotide

treatment inhibited differentiation, it did not prevent growth arrest. Therefore, the differentiation of primary mouse keratinocytes required a function of Kip other than the inhibition of cyclin-associated activities, and we suggest that this requirement may reflect a novel Rb kinase activity present in Kip immune complexes, which is dependent on the presence of cyclin D3. Thus, the placement of keratinocytes in suspension induces a program that includes loss of cyclin activity, which is linked to terminal growth arrest, and an induction of **p27kip1**, which is linked to the differentiation program.

L9 ANSWER 11 OF 33 MEDLINE
ACCESSION NUMBER: 97098827 MEDLINE
DOCUMENT NUMBER: 97098827 PubMed ID: 8943498
TITLE: Angiotensin II-stimulated hypertrophy of LLC-PK1 cells depends on the induction of the **cyclin-dependent kinase** inhibitor **p27Kip1**.
AUTHOR: Wolf G; Stahl R A
CORPORATE SOURCE: Department of Medicine, University of Hamburg, Germany.
SOURCE: KIDNEY INTERNATIONAL, **(1996 Dec)** 50 (6) 2112-9. Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970313
Last Updated on STN: 19970313
Entered Medline: 19970228

AB Angiotensin II (Ang II) induces hypertrophy of cultured proximal tubular epithelial cells including the LLC-PK1 cell line. We have previously shown that this hypertrophy appears in the G1-phase of the cell cycle. Since progression through the cell cycle is controlled by a series of cyclin and **cyclin-dependent kinase** (CdK) complexes that may be inactivated by CdK inhibitors, we studied the expression of the CdK-inhibitor **p27Kip1** in LLC-PK1 cells challenged with Ang II. Compared to cells grown in serum-free medium, Ang II treatment enhanced **p27Kip1** protein, but not mRNA expression. This **p27Kip1** induction was mediated through AT1-receptors. Exogenous TGF-beta also stimulated **p27Kip1** protein expression. Immunoprecipitation experiments revealed that **p27Kip1** preferentially associated with CdK4 in Ang II-treated LLC-PK1 cells and that the activity of this kinase was inhibited after Ang II-treatment, an effect that may be generated by increased **p27Kip1** binding to cyclin D1-CdK4 complexes. In contrast, **p27Kip1** was not associated with cyclin E-CdK2 complexes in Ang II-stimulated cells. Treatment of LLC-PK1 cells with **p27Kip1 antisense**, but not missense, oligonucleotides abolished the Ang II-mediated cell hypertrophy as measured by de novo protein synthesis and total protein content, and facilitated entry into the S-phase of the cell cycle. Our findings suggest that Ang II stimulates **p27Kip1** expression in renal cells. Furthermore, this induction of the CdK-inhibitor appears pivotal in the hypertrophy induced by Ang II and elucidates the molecular mechanisms associated with this growth response in proximal tubular cells.

L9 ANSWER 12 OF 33 MEDLINE
ACCESSION NUMBER: 97054449 MEDLINE
DOCUMENT NUMBER: 97054449 PubMed ID: 8898746
TITLE: Impact of the **cyclin-dependent kinase** inhibitor **p27Kip1** on resistance of tumor cells to anticancer agents.

AUTHOR: St Croix B; Florenes V A; Rak J W; Flanagan M; Bhattacharya N; Slingerland J M; Kerbel R S
CORPORATE SOURCE: Division of Cancer Biology Research, Sunnybrook Health Science Centre, Toronto, Ontario, Canada.
CONTRACT NUMBER: CA 41233 (NCI)
SOURCE: NATURE MEDICINE, **(1996 Nov)** 2 (11) 1204-10.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961203

AB A low proliferating fraction in solid tumors limits the effectiveness of cell cycle-dependent chemotherapeutic agents. To understand the molecular basis of such "kinetic" resistance we cultured tumor cells as multicellular spheroids and examined levels of **p27Kip1**, a **cyclin-dependent kinase** inhibitor known to be upregulated by intercellular contact in normal cells. When transferred from monolayer to three-dimensional culture, a consistent upregulation (up to 15-fold) of p27 protein was observed in a panel of mouse and human carcinoma cell lines. **Antisense**-oligonucleotide-mediated downregulation of p27 in EMT-6 mammary tumor cell spheroids reduced intercellular adhesion, increased cell proliferation, sensitized tumor cells to 4-hydroperoxycyclophosphamide, and restored drug- or radiation-induced cell-cycle perturbations repressed in spheroid culture. Our results implicate p27 as a regulator of drug resistance in solid tumors and suggest that tumor-targeted p27 antagonists may be useful chemosensitizers in conjunction with conventional anticancer therapy.

L9 ANSWER 13 OF 33 MEDLINE
ACCESSION NUMBER: 96324898 MEDLINE
DOCUMENT NUMBER: 96324898 PubMed ID: 8702474
TITLE: Abrogation of **p27Kip1** by cDNA **antisense** suppresses quiescence (G0 state) in fibroblasts.
AUTHOR: Rivard N; L'Allemain G; Bartek J; Pouyssegur J
CORPORATE SOURCE: Centre de Biochimie-CNRS, Universite de Nice, Parc Valrose, 06108 Nice, France.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1996 Aug 2)** 271 (31) 18337-41.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19961008
Last Updated on STN: 19961008
Entered Medline: 19960924

AB Progression of eukaryotic cells through the cell cycle is governed by the sequential formation, activation, and subsequent inactivation of a series of **cyclin-dependent kinase** (Cdk) complexes. p27(Kip1) (p27) is a Cdk inhibitor that blocks, in vitro, the activity of cyclin D-Cdk4, cyclin D-Cdk6, cyclin E-Cdk2 as well as cyclin A-Cdk2, a complex active during S phase. The level of p27 protein expression, usually high in G0/G1 resting cells, declines as cells progress toward S phase and enforced expression of p27 in fibroblasts causes G1 arrest. This situation prevails in CCL39, a Chinese hamster lung fibroblast cell line (this report). However, in addition to p27, several other Cdk inhibitors known to alter G1 progression coexist in most mammalian cells. To

investigate the specific contribution of p27 in the control of the mitogen-sensitive G0/G1 arrest, we specifically reduced its synthesis by expressing a full-length p27 **antisense** cDNA in CCL39 cells. Interestingly, reduction of up to 90% of p27 protein expression increased both basal and serum-stimulated gene transcription of cyclin D1, cyclin A, dihydrofolate reductase, and DNA synthesis reinitiation. Moreover, overexpression of this **antisense** allows cells to grow for several generations in a serum-free medium supplemented with insulin and transferrin only, thus suggesting that p27-depleted cells cannot exit the cell cycle. These effects were fully reversed by coexpression of a plasmid encoding p27 sense. We conclude that p27, by setting the level of growth factor requirement, plays a pivotal role in controlling cell cycle exit, a fundamental step in growth control.

L9 ANSWER 14 OF 33 MEDLINE
ACCESSION NUMBER: 96217948 MEDLINE
DOCUMENT NUMBER: 96217948 PubMed ID: 8629023
TITLE: Requirement of **p27Kip1** for restriction point control of the fibroblast cell cycle.
AUTHOR: Coats S; Flanagan W M; Nourse J; Roberts J M
CORPORATE SOURCE: Department of Basic Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98104, USA.
SOURCE: SCIENCE, **(1996 May 10)** 272 (5263) 877-80. Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960708
Last Updated on STN: 20000303
Entered Medline: 19960627

AB Cells deprived of serum mitogens will either undergo immediate cell cycle arrest or complete mitosis and arrest in the next cell cycle. The transition from mitogen dependence to mitogen independence occurs in the mid-to late G1 phase of the cell cycle and is called the restriction point. Murine Balb/c-3T3 fibroblasts deprived of serum mitogens accumulated the **cyclin-dependent kinase** (CDK) inhibitor **p27Kip1**. This was correlated with inactivation of essential G1 cyclin-CDK complexes and with cell cycle arrest in G1. The ability of specific mitogens to allow transit through the restriction point paralleled their ability to down-regulate p27, and **antisense** inhibition of p27 expression prevented cell cycle arrest in response to mitogen depletion. Therefore, p27 is an essential component of the pathway that connects mitogenic signals to the cell cycle at the restriction point.

L9 ANSWER 15 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:373878 CAPLUS
DOCUMENT NUMBER: 131:168498
TITLE: Effects of **antisense** P21WAF1/CIP1/mda6 expression on the responses of human leukemia cells (U937) to differentiation induction
AUTHOR(S): Wang, Zhiliang; Wang, Shujie; Fisher, Paul; Grant, Steven
CORPORATE SOURCE: Department of Oncology, Henan Medical University, Zhengzhou, 450052, Peop. Rep. China
SOURCE: Henan Yike Daxue Xuebao (**1998**), 33(5), 29-36
CODEN: HEYDE2; ISSN: 1000-1069
PUBLISHER: Henan Yike Daxue Xuebao Bianjibu
DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB To assess the effects of the **cyclin-dependent kinase** inhibitor p21WAF1/CIP1 on PKC activator-induced G1 arrest and differentiation in human myelomonocytic leukemia cells (U937), stable transfectants expressing the p21 coding region in the **antisense** configuration were generated [U937/p21AS(F4) and U937/p21AS(B8)]. Following incubation with phorbol myristate acetate (PMA; 10 nM), U937 p21 **antisense**-expressing cells displayed induction of **p27KIP1** but not of p21, whereas empty vector-contg. cells (U937/pREP4) exhibited induction of both p21 and p27. Compared to controls, PMA-treated U937/p21AS(F4) and U937/p21AS(B8) cells were impaired in G1 arrest, dephosphorylation of the retinoblastoma protein (pRb), redn. in activity of **cyclin-dependent kinase** 2 (CDK2), and acquisition of certain differentiated features (e.g., plastic adherence). The non-tumor promoting PKC activator bryostatin 1 induced p27 but not p21 in control cells and was considerably weaker than PMA in inducing G1 arrest and related events. Nevertheless, dysregulation of p21 in p21AS/F4 and p21AS/B8 cells abrogated the modest effects of bryostatin 1 on cell cycle arrest and cellular maturation. Unexpectedly, dys-regulation of p21 did not modify the net antiproliferative effects of PMA or bryostatin 1. However, p21AS/F4 and p21AS/B8 cells displayed a significant increase in PMA- and bryostatin 1-mediated apoptosis compared to empty vector controls. Thus, p21 plays a crit. role in leukemic cell G1 arrest and differentiation following exposure to PKC activators. They also suggest that following treatment with these agents, dysregulation of p21 may prevent leukemic cells from engaging a normal differentiation program, and instead direct cells along an apoptotic pathway.

L9 ANSWER 16 OF 33 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:245166 CAPLUS

DOCUMENT NUMBER: 130:276731

TITLE: **Cyclin-dependent kinase** inhibitor **p27Kip1** and method for decreasing adhesion-dependent resistance of tumor cells to anticancer agents with **p27Kip1** inhibitors

INVENTOR(S): Kerbel, Robert S.; St. Croix, Brad B.

PATENT ASSIGNEE(S): Can.

SOURCE: Can. Pat. Appl., 52 pp.
CODEN: CPXXEB

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2196727	AA	19980316	CA 1997-2196727	19970204 <--

PRIORITY APPLN. INFO.: US 1996-26143P P 19960916

AB The invention increases the effectiveness of chemotherapeutic agents in treating solid tumor cells. The **cyclin-dependent kinase** inhibitor **p27Kip1** is a major regulator of the drug resistance of solid tumors, and resistance is increased by high levels of intracellular **p27Kip1**. Tumor-targeted **p27Kip1** inhibitors are therefore useful as chemosensitizers in treatment of slow-growing solid tumors. The invention relates to products which are **p27Kip1** inhibitors that can downregulate or inactivate **p27Kip1**, decrease cell adhesion, increase cell proliferation, increase susceptibility to spontaneous or drug- or irradn.-induced cell death and reduce or prevent tumor resistance to anticancer compds. These products may be used in pharmaceutical compns. The invention also relates

to the use of the **p27Kip1** inhibitor and a method for using **p27Kip1** inhibitor as a chemosensitizer and a regulator of drug resistance of solid tumors. The invention includes a method for screening anti-cancer agents which are preferentially active against slowly dividing cells or which chemosensitize solid tumors. The **p27Kip1** inhibitor may be e.g. an **antisense** oligonucleotide or peptide antagonist.

L9 ANSWER 17 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:711774 CAPLUS
DOCUMENT NUMBER: 130:76801
TITLE: Reduction in levels of the **cyclin-dependent kinase** inhibitor p27kip-1 coupled with transforming growth factor .beta. neutralization induces cell-cycle entry and increases retroviral transduction of primitive human hematopoietic cells
AUTHOR(S): Dao, Mo A.; Taylor, Naomi; Nolta, Jan A.
CORPORATE SOURCE: Division of Research Immunology/Bone Marrow Transplantation, Childrens Hospital Los Angeles, CA, 90027, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(22), 13006-13011
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Successful gene therapy depends on stable transduction of hematopoietic stem cells. Target cells must cycle to allow integration of Moloney-based retroviral vectors, yet hematopoietic stem cells are quiescent. Cells can be held in quiescence by intracellular **cyclin-dependent kinase** inhibitors. The **cyclin-dependent kinase** inhibitor p15INK4B blocks assocn. of **cyclin-dependent kinase** (CDK)4/cyclin D and p27kip-1 blocks activity of CDK2/cyclin A and CDK2/cyclin E, complexes that are mandatory for cell-cycle progression. Antibody neutralization of .beta. transforming growth factor (TGF.beta.) in serum-free medium decreased levels of p15INK4B and increased colony formation and retroviral-mediated transduction of primary human CD34+ cells. Although TGF.beta. neutralization increased colony formation from more primitive, noncycling hematopoietic progenitors, no increase in M-phase-dependent, retroviral-mediated transduction was obsd. Transduction of the primitive cells was augmented by culture in the presence of **antisense** oligonucleotides to p27kip-1 coupled with TGF.beta.-neutralizing antibodies. The transduced cells engrafted immune-deficient mice with no alteration in human hematopoietic lineage development. The authors conclude that neutralization of TGF.beta., plus redn. in levels of the **cyclin-dependent kinase** inhibitor p27, allows transduction of primitive and quiescent hematopoietic progenitor populations.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 18 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:699412 CAPLUS
DOCUMENT NUMBER: 130:50360
TITLE: Regulation of exit from quiescence by p27 and cyclin D1-CDK4

AUTHOR(S): Ladha, Mohamed H.; Lee, Kwang Y.; Upton, Todd M.; Reed, Michael F.; Ewen, Mark E.
CORPORATE SOURCE: The Dana-Farber Cancer Institute and the Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Molecular and Cellular Biology (**1998**), 18(11), 6605-6615
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The synthesis of cyclin D1 and its assembly with **cyclin-dependent kinase** 4 (CDK4) to form an active complex is a rate-limiting step in progression through the G1 phase of the cell cycle. Using an activated allele of mitogen-activated protein kinase kinase 1 (MEK1), we show that this kinase plays a significant role in pos. regulating the expression of cyclin D1. This was found both in quiescent serum-starved cells and in cells expressing dominant-neg. Ras. Despite the observation that cyclin D1 is a target of MEK1, in cycling cells, activated MEK1, but not cyclin D1, is capable of overcoming a G1 arrest induced by Ras inactivation. Either wild-type or catalytically inactive CDK4 cooperates with cyclin D1 in reversing the G1 arrest induced by inhibition of Ras activity. In quiescent NIH 3T3 cells expressing either ectopic cyclin D1 or activated MEK1, cyclin D1 is able to efficiently assoc. with CDK4; however, the complex is inactive. A significant percentage of the cyclin D1-CDK4 complexes are assocd. with p27 in serum-starved activated MEK1 or cyclin D1 cell lines. Redn. of p27 levels by expression of **antisense** p27 allows for S-phase entry from quiescence in NIH 3T3 cells expressing ectopic cyclin D1, but not in parental cells.
REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 19 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:672262 CAPLUS
DOCUMENT NUMBER: 130:36239
TITLE: STAT3 activation accompanies keratinocyte differentiation
AUTHOR(S): Hauser, Paul J.; Agrawal, Deepak; Hackney, Jason; Pledger, Warren J.
CORPORATE SOURCE: Department of Cell Biology, Vanderbilt University, Nashville, TN, 37240, USA
SOURCE: Cell Growth & Differentiation (**1998**), 9(10), 847-855
CODEN: CGDIE7; ISSN: 1044-9523
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The signal transducers and activators of transcription (STAT) family of transcription factors has been demonstrated to play key roles in a variety of cell types under conditions that promote differentiation or cell cycle exit. We report our studies of primary murine keratinocytes in which we demonstrate activation of STAT3 during growth arrest and differentiation. In adherent cells, STAT3-specific DNA binding activity was detected in quiescent cultures, down-regulated upon mitogenic stimulation, and found to reaccumulate as cells reentered quiescence. Suspension culturing of proliferating keratinocytes, which induces differentiation, also resulted in induction of STAT3 activity. Furthermore, induction of STAT3 after suspension culturing did not occur in MK cells, an immortalized murine keratinocyte cell line that does not undergo differentiation. Because STAT3 activation in these cells corresponded tightly with the growth status, we examd. whether there was a relationship between the cell cycle machinery and STAT3 activation by inhibiting **p27kip1**

accumulation, which is obsd. during growth arrest, with **antisense** oligonucleotides and by using keratinocytes lacking functional **p27kip1**. In both cases, there was a loss of STAT3 activation and a concomitant delay in terminal cell cycle withdrawal and in the expression of the differentiation specific marker, keratin 1. Thus, in addn. to controlling transcription mediated through E2F, our data demonstrate that alterations in the cell cycle machinery are required for appropriate up-regulation of STAT3 activity that occurs during keratinocyte differentiation.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:671514 CAPLUS

DOCUMENT NUMBER: 130:36575

TITLE: Evidence of a functional role for the **cyclin-dependent kinase** inhibitor p21WAF1/CIP1/MDA6 in the reciprocal regulation of PKC activator-induced apoptosis and differentiation in human myelomonocytic leukemia cells

AUTHOR(S): Wang, Zhiliang; Su, Zao-Zhong; Fisher, Paul B.; Wang, Shujie; VanTuyle, Glenn; Grant, Steven

CORPORATE SOURCE: Department of Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, 23298, USA

SOURCE: Experimental Cell Research (**1998**), 244(1), 105-116
CODEN: ECREAL; ISSN: 0014-4827

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The functional role of the **cyclin-dependent kinase** inhibitor p21WAF1/CIP1 in leukemic cell G1 arrest, differentiation, and apoptosis induced by two PKC activators (PMA and bryostatin 1) was examd. using **antisense**-expressing lines [U937/p21AS(F4) and U937/p21AS(B8)]. Following incubation with 10 nM PMA (24 h), **antisense**-expressing cells displayed induction of **p27KIP1** but not of p21, whereas empty vector-contg. cells (U937/pREP4) exhibited induction of both p21 and p27. **Antisense**-expressing cells were impaired in G1 arrest, dephosphorylation of the retinoblastoma protein, dephosphorylation and redn. in activity of **cyclin-dependent kinase** 2, and acquisition of differentiated features (e.g., plastic adherence). Bryostatin 1 induced p27 but not p21 in control cells and was less effective than PMA in initiating G1 arrest and related events. Nevertheless, disruption of p21 expression abrogated the effects of bryostatin 1 on cell cycle arrest and cellular maturation. Dysregulation of p21 did not, however, modify PMA- or bryostatin 1-mediated downregulation of c-Myc protein. Unexpectedly, disruption of p21 failed to attenuate the net redn. in viable cell no. following PMA or bryostatin 1 treatment inasmuch as impaired differentiation was accompanied by a lowered threshold for PMA- and bryostatin 1-induced apoptosis. Inhibition of p21 expression also promoted PMA- and bryostatin 1-mediated loss of mitochondrial transmembrane potential (.DELTA..psi.m) and release of cytochrome c into the cytosol. Together, these findings demonstrate a crit. functional role for p21 in regulating myelomonocytic leukemic cell G1 arrest and differentiation following exposure to two PKC activators exhibiting disparate patterns of activity. They also suggest that following treatment with these agents, dysregulation of p21 prevents leukemic cells from engaging a normal differentiation program through a c-Myc-independent mechanism, and instead directs cells along an apoptotic pathway. (c) 1998

Academic Press.
REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:622376 CAPLUS
DOCUMENT NUMBER: 129:312411
TITLE: Human CUL11 associates with the SKP1/SKP2 complex and regulates p21CIP1/WAF1 and cyclin D proteins
AUTHOR(S): Yu, Zhong-Kang; Gervais, Jennifer M.; Zhang, Hui
CORPORATE SOURCE: Department of Genetics, Yale University School of Medicine, New Haven, CT, 06520, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(19), 11324-11329
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Deregulation of cell proliferation is a hallmark of cancer. In many transformed cells, the cyclin A/CDK2 complex that contains S-phase kinase assocd. proteins 1 and 2 (SKP1 and SKP2) is highly induced. To det. the roles of this complex in the cell cycle regulation and transformation, we have examd. the compn. of this complex. We report here that this complex contained an addnl. protein, human CUL-1, a member of the cullin/CDC53 family. The identification of CUL-1 as a member of the complex raises the possibility that the p19SKP1/p45SKP2/CUL-1 complex may function as the yeast SKP1-CDC53-F-box (SCF) protein complex that acts as a ubiquitin E3 ligase to regulate the G1/S transition. In mammalian cells, cyclin D, p21CIP1/WAF1, and **p27KIP1** are short-lived proteins that are controlled by ubiquitin-dependent proteolysis. To det. the potential in vivo targets of the p19SKP1/p45SKP2/CUL-1 complex, we have used the specific **antisense** oligodeoxynucleotides against either SKP1, SKP2, or CUL-1 RNA to inhibit their expression. Treatment of cells with these oligonucleotides caused the selective accumulation of p21 and cyclin D proteins. The protein level of p27 was not affected. These data suggest that the human p19SKP1/p45SKP2/CUL-1 complex is likely to function as an E3 ligase to selectively target cyclin D and p21 for the ubiquitin-dependent protein degrdn. Aberrant expression of human p19SKP1/p45SKP2/CUL-1 complex thus may contribute to tumorigenesis by regulating the protein levels of G1 cell cycle regulators.

L9 ANSWER 22 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:434794 CAPLUS
DOCUMENT NUMBER: 129:160013
TITLE: **Antisense** telomerase treatment: induction of two distinct pathways, apoptosis and differentiation
AUTHOR(S): Kondo, Seiji; Tanaka, Yoshikazu; Kondo, Yasuko; Hitomi, Masahiro; Barnett, Gene H.; Ishizaka, Yukihito; Liu, Jinbo; Haqqi, Talat; Nishiyama, Akiko; Villeponteau, Bryant; Cowell, John K.; Barna, Barbara P.
CORPORATE SOURCE: Department of Neurosurgery, Brain Tumor/Neuro-Oncology Center, The Cleveland Clinic Foundation, Cleveland, OH, 44195, USA
SOURCE: FASEB Journal (**1998**), 12(10), 801-811
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Telomerase, the enzyme that elongates telomeric DNA (TTAGGG)n, may be involved in cellular immortality and oncogenesis. To investigate the effect of inhibition of telomerase on tumor cells, we transfected the **antisense** vector against the human telomerase RNA into human malignant glioma cells exhibiting telomerase activity. After 30 doublings, some subpopulations of transfectants expressed a high level of interleukin-1.beta.-converting enzyme (ICE) protein and underwent apoptosis. In contrast, other subpopulations also showed enhanced ICE protein but escaped from apoptotic crisis and continued to grow, although their DNA synthesis, invasive ability, and tumorigenicity in nude mice were significantly reduced. Surviving cells demonstrated increased expression of glial fibrillary acidic protein and decreased motility, consistent with a more differentiated state. These cells also contained enhanced expression of the **cyclin-dependent kinase** inhibitors (CDKIs) p21 and p27. Treatment of surviving nonapoptotic cells with **antisense** oligonucleotides against p27, but not p21, induced apoptotic cell death, suggesting that p27 may have protected differentiating glioma cells from apoptosis. These data show that treatment with **antisense** telomerase inhibits telomerase activity and subsequently induces either apoptosis or differentiation. Regulation of these two distinct pathways may be dependent on the expression of ICE or CDKIs.

L9 ANSWER 23 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:383109 CAPLUS
DOCUMENT NUMBER: 129:120614
TITLE: Astrocyte progression from G1 to S phase of the cell cycle depends upon multiple protein interaction
AUTHOR(S): Pedram, Ali; Razandi, Mahnaz; Hu, Ren-Ming; Levin, Ellis R.
CORPORATE SOURCE: Division of Endocrinology, Veteran Affairs Medical Center, Long Beach, CA, 90822, USA
SOURCE: Journal of Biological Chemistry (**1998**), 273(22), 13966-13972
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The proliferation of cultured astrocytes is pos. and neg. regulated, resp., by the endogenous neuropeptides, endothelin-3 (ET-3) and atrial natriuretic peptide (ANP). Here, we detd. the important steps for the modulation by ET and ANP of G1 to S phase cell cycle progression. ET-3 stimulated an increased no. of fetal rat diencephalic astrocytes to progress through G1/S, and this was blocked significantly by ANP. ET augmented the gene expression and/or protein prodn. of D-type, A and E cyclins, whereas ANP inhibited these events significantly. ET also stimulated the activation of the cyclin-dependent kinases Cdk2, Cdk4, and Cdk6, directed against the retinoblastoma protein pRb, and this was inhibited by as much as 80% by ANP. As an addnl. mechanism of cell cycle restraint, ANP stimulated the prodn. of multiple **cyclin-dependent kinase** inhibitory (CKI) proteins, including p16, p27, and p57. This was crit. because **antisense** oligonucleotides to each CKI reversed ANP-induced inhibition of ET-stimulated DNA synthesis by as much as 85%. CKI **antisense** oligonucleotides also reversed the ANP inhibition of Cdk phosphorylation of pRb. In turn, ET inhibited ANP-stimulated prodn. of the CKIs, thereby promoting cell cycle progression. Specific and changing assocns. of the CKI with Cdk2 and Cdk4 were stimulated by ANP and inhibited by ET. Our findings identify several mechanisms by which endogenous modulators of astrocyte proliferation can control the G1-S progression and indicate that multiple CKIs are necessary to restrain cell cycle progression in these cells.

L9 ANSWER 24 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:338996 CAPLUS
DOCUMENT NUMBER: 129:90853
TITLE: Distinct roles of the co-activators p300 and CBP in retinoic-acid-induced F9-cell differentiation
AUTHOR(S): Kawasaki, Hiroaki; Eckner, Richard; Yao, Tso-Pang; Taira, Kazunari; Chiu, Robert; Livingston, David M.; Yokoyama, Kazunari K.
CORPORATE SOURCE: Tsukuba Life Science Center, Inst. Phys. and Chemical Res., Tsukuba Science City, 305-0074, Japan
SOURCE: Nature (London) (**1998**), 393(6682), 284-289
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The related proteins p300 and CBP (cAMP-response-element-binding protein (CREB)-binding protein) are transcriptional co-activators that act with other factors to regulate gene expression and play roles in many cell-differentiation and signal transduction pathways. Both proteins have intrinsic histone-acetyltransferase activity and may act directly on chromatin, of which histone is a component, to facilitate transcription. They are also involved in growth control pathways, as shown by their interaction with the tumor suppressor p53 and the viral oncogenes E1A and SV40 T antigen. Here the authors report functional differences of p300 and CBP in vivo. The authors examd. their roles during retinoic-acid-induced differentiation, cell-cycle exit and programmed cell death (apoptosis) of embryonal carcinoma F9 cells, using hammerhead **ribozymes** capable of cleaving either p300 or CBP mRNAs. F9 cells expressing a p300-specific **ribozyme** became resistant to retinoic-acid-induced differentiation, whereas cells expressing a CBP-specific **ribozyme** were unaffected. Similarly, retinoic-acid-induced transcriptional upregulation of the cell-cycle inhibitor p21 required normal levels of p300, but not CBP, whereas the reverse was true for p27. In contrast, both **ribozymes** blocked retinoic-acid-induced apoptosis, indicating that both co-activators are required for this process. Thus, despite their similarities, p300 and CBP have distinct functions during retinoic-acid-induced differentiation of F9 cells.

L9 ANSWER 25 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:233046 CAPLUS
DOCUMENT NUMBER: 128:306965
TITLE: Differential role for protein kinase C-mediated signaling in the proliferation of medulloblastoma cell lines
AUTHOR(S): Adesina, Adekunle M.; Dooley, Nora; Yong, Voon-Wee; Nalbantoglu, Josephine
CORPORATE SOURCE: Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73104, USA
SOURCE: International Journal of Oncology (**1998**), 12(4), 759-768
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent studies have implicated protein kinase C (PKC)-mediated signaling in the proliferation of gliomas. In this study, the authors have investigated the role of PKC mediated signaling in the proliferation of medulloblastoma cell lines DAOY, D283-Med and D341-Med. By Western blot

analyses, conventional PKC (cPKC) .alpha. was detectable in DAOY only, while atypical PKC (aPKC) .zeta. was present in all three cell lines, cPKC .beta.1, .beta.11, .gamma., novel PKC (nPKC) .delta., and .epsilon. were not detectable in any of the cell lines. **Antisense** oligonucleotides to PKC .alpha., Calphostin C (a specific PKC inhibitor) and prolonged treatment with phorbol 12-myristate 13-acetate (PMA) with down regulation of cPKC .alpha. caused a decrease in proliferation in DAOY and no effect on D283-Med. Furthermore, PMA treatment was also assocd. with upregulation of p21cip1 in DAOY. Since cPKC .alpha. is the only PMA responsive isoform in DAOY, this observation implicates the cPKC .alpha. isoform in the proliferation of DAOY but not in D283-Med. A comparison of DAOY and D283-Med showed a higher proliferation index in DAOY. In contrast, multiprobe riboquant RNase protection assay revealed higher levels of **p27kip1** and p21cip1 mRNA in D283-Med. These transcripts were barely detectable in untreated DAOY. These observations indicate possible significant mol. heterogeneity among medulloblastomas with implications for differing biol. among medulloblastoma cell lines and tumors.

L9 ANSWER 26 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:77917 CAPLUS
DOCUMENT NUMBER: 128:203656
TITLE: Effects of **antisense** p21 (WAF1/CIP1/MDA6) expression on the induction of differentiation and drug-mediated apoptosis in human myeloid leukemia cells (HL-60)
AUTHOR(S): Freemerman, A. J.; Vrana, J. A.; Tombes, R. M.; Jiang, H.; Chellappan, S. P.; Fisher, P. B.; Grant, S.
CORPORATE SOURCE: Department of Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, 23298-0230, USA
SOURCE: Leukemia (**1997**), 11(4), 504-513
CODEN: LEUKED; ISSN: 0887-6924
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The p21MDA6 gene product induces cell cycle arrest in p53-null human leukemic cells exposed to differentiation stimuli. The authors employed an HL-60 cell line stably transfected with a p21MDA6 **antisense** construct to compare the effects of p21MDA6 dysregulation on the response of myeloid leukemia cells to differentiating and cytotoxic agents. **Antisense**-expressing cells (HL-60/AS5) treated with 5 nM PMA for 24 h exhibited attenuated induction of p21MDA6 compared to empty vector controls (HL-60/V2). This phenomenon was accompanied by a redn. in the percentage of cells undergoing G1 arrest (67.6 vs. 82.9) and expressing the monocytic maturation marker CD11b (35.5 vs. 50.5). Although HL-AS5 and HL-60/V2 cells did not exhibit obvious differences in the phosphorylation status of the retinoblastoma protein (pRB), in E2F complex formation, or in **p27kip1** induction following PMA exposure, inhibition of activity of **cyclin-dependent kinase**-2 was attenuated in the **antisense**-expressing line. A 24-h exposure to 5 nM PMA also reduced the cloning efficiency of HL-60/V2 cells to a significantly greater extent than HL-60/AS5 cells (ie to 30.1 vs. 57.2 of controls). In contrast to the disparate responses to PMA, HL-60/AS5 and HL-60/V2 cells treated with the antimetabolite 1-.beta.-D-arabinofuranosylcytosine (Ara-C; 10 .mu.M for 6 h) displayed equal susceptibility to G1 arrest, apoptosis, and inhibition of clonogenicity, phenomena unaccompanied by p21MDA6 and **p27kip1** induction, or pRB dephosphorylation. These observations indicate that dysregulation of p21MDA6 in p53-null human myeloid leukemia cells

interferes with PMA-related G1 arrest, CDK-2 inhibition, differentiation, and loss of clonogenic survival in the absence of obvious alterations in pRB phosphorylation status or E2F complex formation. They also provide functional evidence that p21MDA6 induction does not appear to be required for Ara-C-induced apoptosis, G1 arrest, or the resulting redn. in the self-renewal capacity of HL-60 cells.

L9 ANSWER 27 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:34107 CAPLUS
DOCUMENT NUMBER: 128:188443
TITLE: The upregulation of **p27Kip1** by rapamycin results in G1 arrest in exponentially growing T-cell lines
AUTHOR(S): Kawamata, Shin; Sakaida, Hitoshi; Hori, Toshiyuki; Maeda, Michiyuki; Uchiyama, Takashi
CORPORATE SOURCE: Institute for Virus Research, Chest Disease Research Institute, Kyoto University, Kyoto, 606, Japan
SOURCE: Blood (**1998**), 91(2), 561-569
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An immunosuppressant Rapamycin (Rap) has been reported to cause G1 arrest by inhibiting p70 S6 kinase and G1 cyclin/cdks kinase activities when added to quiescent cells with mitogens. However, antiproliferative effects of Rap on exponentially growing cells have been poorly investigated. We examd. the intracellular events after the treatment of Rap in exponentially growing T cells and found that Rap upregulated a cdks inhibitor, **p27Kip1** at both mRNA and protein levels in Rap-sensitive cells. Antiproliferative effect of Rap was mainly ascribed to the inhibition of cyclin E/cdk2 kinase activity through the formation of cyclin E/cdk2-**p27Kip1** complex rather than inhibition of p70 S6 kinase activity. Furthermore, we showed that Rap-sensitive cells with elevated **p27Kip1** expression lost sensitivity to Rap when **antisense p27Kip1** was introduced, which indicates that the basal level of **p27Kip1** is one of the limiting factors that det. the sensitivity to Rap in already cycling cells. These data suggest the presence of a putative threshold level of **p27Kip1** at late G1 phase in already cycling cells. Rap may cause G1 arrest by upregulating the amt. of **p27Kip1** beyond the threshold in some Rap-sensitive cells that are exponentially growing.

L9 ANSWER 28 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:25007 CAPLUS
DOCUMENT NUMBER: 128:87112
TITLE: Disorders in cell circuitry associated with multistage carcinogenesis: exploitable targets for cancer prevention and therapy
AUTHOR(S): Weinstein, I. Bernard; Begemann, Martin; Zhou, Ping; Han, Edward K. -H.; Sgambato, Alessandro; Doki, Yuichiro; Arber, Nadir; Ciaparrone, Marco; Yamamoto, Hirofumi
CORPORATE SOURCE: Herbert Irving Comprehensive Cancer Center, Columbia University College of Physicians and Surgeons, New York, NY, 10032, USA
SOURCE: Clinical Cancer Research (**1997**), 3(12, Pt. 2), 2696-2702
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 51 refs. The development of a malignant tumor involves the progressive acquisition of mutations and epigenetic abnormalities in

multiple genes that have highly diverse functions. Some of these genes code for pathways of signal transduction that mediate the action of growth factors. The enzyme protein kinase C plays an important role in these events and in the process of tumor promotion. Therefore, the authors examd. the effects of three inhibitors of protein kinase C, CGP 41251, RO 31-8220, and calphostin C, on human glioblastoma cells. These compds. inhibited growth and induced apoptosis; these activities were assocd. with a decrease in the level of CDC2 and cyclin B1/CDC2-assocd. kinase activity. This may explain why the treated cells accumulated in G2-M. In a sep. series of studies, the authors examd. abnormalities in cell cycle control genes in human cancer. The authors have found that cyclin D1 is frequently overexpressed in a variety of human cancers. Mechanistic studies indicate that cyclin D1 can play a crit. role in carcinogenesis because: overexpression enhances cell transformation and tumorigenesis; introduction of an **antisense** cyclin D1 cDNA into either human esophageal or colon cancer cells reverts their malignant phenotype; and overexpression of cyclin D1 can enhance the amplification of other genes. The latter finding suggests that cyclin D1 can enhance genomic instability and, thereby, the process of tumor progression. Therefore, inhibitors of the function of cyclin D1 may be useful in both cancer chemoprevention and therapy. The authors obtained evidence for the existence of homeostatic feedback loops between cyclins D1 or E and the cell cycle inhibitory protein **p27Kip1**. On the basis of these and other findings, the authors hypothesize that, because of their disordered circuitry, cancer cells suffer from "gene addiction" and "gene hypersensitivity," disorders that might be exploited in both cancer prevention and therapy.

L9 ANSWER 29 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:669781 CAPLUS
DOCUMENT NUMBER: 127:317873
TITLE: Role of c-myc and p27 in anti-IgM induced B-lymphoma apoptosis
AUTHOR(S): Scott, D. W.; Donjerkovic, D.; Maddox, B.; Ezhevsky, S.; Grdina, T.
CORPORATE SOURCE: Holland Laboratory for the Biomedical Sciences, Department of Immunology, Rockville, MD, 20855, USA
SOURCE: Current Topics in Microbiology and Immunology (**1997**), 224(C-Myc in B-Cell Neoplasia), 103-112
CODEN: CTMIA3; ISSN: 0070-217X
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Crosslinking membrane IgM receptors on a set of murine B cell lymphomas leads to a rapid increase in c-myc, followed by a decrease in its expression to undetectable levels by 8-24 h. These cells die soon thereafter via apoptosis. IgD receptor crosslinking also leads to an increase in c-myc expression, but it remains above baseline levels for >24 h; these cells continue to proliferate and do not die. The authors previously reported that **antisense** oligonucleotides for c-myc prevented growth arrest and cell death in these lymphomas, independent of the presence of mitogenic CpG motifs. Indeed, **antisense** for c-myc actually led to a stabilization of c-myc message and protein. Growth arrest in these cells is dependent on the increased synthesis of the p27 cyclin kinase inhibitor (Kip1) normally induced after anti-IgM crosslinking. Consistent with its biol. effects, anti-IgD does not cause an increase in p27. Since dexamethasone causes a loss of myc and synergizes with the anti-IgM signal, the authors suggest that accelerated cell death with this steroid in the presence of anti-IgM is due to a more rapid degrdn. of this oncogene product. Finally, the authors propose that

c-myc drives the transcription or activation of an inhibitor of the p27 Kip (Kipi). Hence, loss of c-myc in response to anti-IgM signals in these B-cell lymphomas leads to upregulation of p27, growth arrest, and apoptosis. It follows that maintenance of c-myc in these B-cell lymphomas should lead to survival and no increase in p27.

L9 ANSWER 30 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:633478 CAPLUS
DOCUMENT NUMBER: 127:317583
TITLE: High glucose stimulates expression of **p27Kip1** in cultured mouse mesangial cells: relationship to hypertrophy
AUTHOR(S): Wolf, Gunter; Schroeder, Regine; Ziyadeh, Fuad N.; Thaiss, Friedrich; Zahner, Gunther; Stahl, Rolf A. K.
CORPORATE SOURCE: Dep. Medicine, Division Nephrology and Osteology, Univ. Hamburg, Hamburg, D-20246, Germany
SOURCE: American Journal of Physiology (**1997**), 273(3, Pt. 2), F348-F356
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hypertrophy of mesangial cells is an early hallmark of diabetic nephropathy. The authors have previously shown that murine mesangial cells (MMC), cultured in high-glucose medium, are arrested in the G1 phase of the cell cycle and undergo hypertrophy. This study was undertaken to test whether high glucose-contg. medium influences the expression of **p27Kip1**, an inhibitor of G1 phase active cyclin-dependent kinases (CDK). Incubation of MMC, in the absence of other factors for 48-96 h, in medium contg. high D-glucose (450 mg/dL), stimulated **p27Kip1** protein expression but failed to influence mRNA abundance. These effects were independent of the osmolarity of the medium. High glucose-stimulated expression of **p27Kip1** involved activation of protein kinase C and was partly dependent on induction of transforming growth factor-.beta. (TGF-.beta.). Immunopptn. expts. revealed that only small amts. of **p27Kip1** protein from MMC grown in high-glucose medium preferentially assocs. with CDK2 but not with CDK4. The **p27Kip1** **antisense**, but not missense, oligonucleotides inhibited high glucose-stimulated total protein synthesis and facilitated G1 phase exit. The data showed for the first time that expression of **p27Kip1** protein is pivotal in mesangial cell hypertrophy induced by high ambient glucose. These findings may be important in the deciphering of mol. processes causing diabetic glomerular hypertrophy.

L9 ANSWER 31 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:254722 CAPLUS
DOCUMENT NUMBER: 126:288546
TITLE: Mesangial cell proliferation mediated by PDGF and bFGF is determined by levels of the cyclin kinase inhibitor **p27Kip1**
AUTHOR(S): Shankland, Stuart J.; Pippin, Jeffrey; Flanagan, Mike; Coats, Steve R.; Nangaku, Masaomi; Gordon, Katherine L.; Roberts, James M.; Couser, William G.; Johnson, Richard J.
CORPORATE SOURCE: Dep. Nephrology, Univ. Washington, Seatlle, WA, USA
SOURCE: Kidney International (**1997**), 51(4), 1088-1099

CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mesangial cell proliferation in vitro is regulated by many cytokines. Platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) are potent mesangial cell mitogens, whereas transforming growth factor-.beta.1 (TGF-.beta.1) reduces their effects. We examd. how these cytokines regulate rat mesangial cell proliferation at the level of the cell-cycle. Quiescent mesangial cells in vitro express the cyclin kinase inhibitor, **p27Kip1** (p27), and PDGF- and bFGF-induced mesangial cell proliferation is assocd. with a substantial decrease in p27 levels. Consequently there is a marked increase in expression (Western blot anal., immunostaining) of cyclin A and CDK2. The decline in p27 levels was prevented by TGF-.beta.1 during inhibition of PDGF- and bFGF-induced mesangial cell proliferation. To det. the functional role of p27 during cytokine-mediated mesangial cell proliferation, the expression of p27 was reduced with specific **p27Kip1 antisense** oligodeoxynucleotides. Reducing the levels of p27 resulted in an increased magnitude of mesangial cell proliferation (BrdU and 3H-thymidine incorporation) induced by PDGF and bFGF compared to non-transfected mesangial cells and mesangial cells transfected with control mismatch oligodeoxynucleotides. Furthermore, the onset of maximal proliferation occurred earlier in mesangial cells transfected with **antisense** compared to control. The redn. in proliferation by TGF-.beta.1 were not altered by decreased p27 expression. Reducing p27 expression in the absence of mitogens was not assocd. with entry into the cell-cycle. These results suggest cytokine mediated mesangial cell proliferation is assocd. with specific cell-cycle proteins, and that the levels of p27 may be important in detg. the mesangial cell's proliferative response to PDGF and bFGF in vitro.

L9 ANSWER 32 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:443586 CAPLUS
DOCUMENT NUMBER: 125:106277
TITLE: Detection of p27/Kip1 mRNA in blood cells by nonradioactive ribonuclease protection assay
AUTHOR(S): Okamoto, Yasuyuki; Nakabayashi, Hitomi; Kikukawa, Seiji; Nakano, Hiroshi
CORPORATE SOURCE: Japan
SOURCE: Rinsho Byori (**1996**), 44(5), 483-486
CODEN: RBYOAI; ISSN: 0047-1860
PUBLISHER: Rinsho Byori Kankokai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Cyclin and **cyclin-dependent kinase** (cdk) complexes, and their inhibitors (CKIs) play important roles in growth regulation on the cells. P27/Kip1 is a CKI assocd. with G1 arrest induced by cell to cell contact, transforming growth factor-.beta. and cAMP. The abnormality of p27/Kip1 genes in human tumors usually appears as a steady level defect of expression, since mutations in them is rare. Thus, it is important to est. the expression level of this gene. To detect the change of p27/Kip1 mRNA level in blood cells, we developed the RNase protection assay using nonradioactive riboprobe which was produced by reverse transcriptase-polymerase chain reaction (RT-PCR) with T7 promoter-added **antisense** primer and the in vitro transcription system. Our assay may be useful for clin. evaluation of the mRNA level.

L9 ANSWER 33 OF 33 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:182273 CAPLUS

DOCUMENT NUMBER: 124:285295
TITLE: The **cyclin-dependent kinase** inhibitor p21WAF1 is required for survival of differentiating neuroblastoma cells
AUTHOR(S): Poluha, Wojciech; Poluha, Dorota K.; Chang, Baochong; Crosbie, Nancy E.; Schonhoff, Christopher M.; Kilpatrick, Daniel L.; Ross, Alonzo H.
CORPORATE SOURCE: Worcester Found. Biomed. Res., Shrewsbury, MA, 01545, USA
SOURCE: Mol. Cell. Biol. (**1996**), 16(4), 1335-41
CODEN: MCEBD4; ISSN: 0270-7306
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We are employing recent advances in the understanding of the cell cycle to study the inverse relationship between proliferation and neuronal differentiation. Nerve growth factor and aphidicolin, an inhibitor of DNA polymerases, synergistically induce neuronal differentiation of SH-SY5Y neuroblastoma cells and the expression of p21WAF1, an inhibitor of cyclin-dependent kinases. The differentiated cells continue to express p21WAF1, even after removal of aphidicolin from the culture medium. The p21WAF1 protein coimmunoppts. with cyclin E and inhibits cyclin E-assocd. protein kinase activity. Each of three **antisense** oligonucleotides complementary to p21WAF1 mRNA partially blocks expression of p21WAF1 and promotes programmed cell death. These data indicate that p21WAF expression is required for survival of these differentiating neuroblastoma cells. Thus, the problem of neuronal differentiation can now be understood in the context of neg. regulators of the cell cycle.

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=> e lowenheim ?/au

E1            2     LOWENHECK KONRAD/AU
E2            1     LOWENHECK M/AU
E3            0 --> LOWENHEIM ?/AU
E4            1     LOWENHEIM A/AU
E5           13     LOWENHEIM F A/AU
E6           39     LOWENHEIM FREDERICK A/AU
E7           38     LOWENHEIM FREDERICK ADOLPH/AU
E8            2     LOWENHEIM FREDERICK W/AU
E9            1     LOWENHEIM GERHARD/AU
E10          23     LOWENHEIM H/AU
E11           4     LOWENHEIM HUBERT/AU
E12           5     LOWENHEIM M/AU

=> s e10-e11

L10          27 ("LOWENHEIM H"/AU OR "LOWENHEIM HUBERT"/AU)

=> dup rem l10

PROCESSING COMPLETED FOR L10
L11          17 DUP REM L10 (10 DUPLICATES REMOVED)

=> d l11 ibib abs tot
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L11 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:42994 CAPLUS
TITLE: Stimulation of cellular regeneration and differentiation in the inner ear
INVENTOR(S): Kil, Jonathan; Gu, Rendu; Grigeur, Corinne; **Lowenheim, Hubert**
PATENT ASSIGNEE(S): Otogene USA, Inc., USA; Otogene, AG

SOURCE: PCT Int. Appl.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002004605	A2	20020117	WO 2001-US21793	20010710
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001088219	A5	20020121	AU 2001-88219	20010710

PRIORITY APPLN. INFO.: US 2000-614099 A 20000711
WO 2001-US21793 W 20010710

AB The present invention provides methods for stimulating the formation of inner ear cells, including inner ear sensory hair cells and inner ear support cells. The methods of the present invention damage and/or kill inner ear cells, and stimulate the formation of new, inner ear cells.

L11 ANSWER 2 OF 17 MEDLINE
ACCESSION NUMBER: 2002156022 IN-PROCESS
DOCUMENT NUMBER: 21882463 PubMed ID: 11887794
TITLE: Transtympanic endoscopy for drug delivery to the inner ear using a new microendoscope.
AUTHOR: Plontke Stefan K R; Plinkert Peter K; Plinkert Beate; Koitschev Assen; Zenner Hans-Peter; **Lowenheim Hubert**
CORPORATE SOURCE: Department of Otorhinolaryngology, Head and Neck Surgery, University of Tubingen, Germany.
SOURCE: ADVANCES IN OTO-RHINO-LARYNGOLOGY, (2002) 59 149-55.
Journal code: 0242534. ISSN: 0065-3071.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020313
Last Updated on STN: 20020313

AB Anatomic variations of the round window (RW) niche found in approximately 33% of human temporal bones may account for some ofthe problems associated with local drug delivery to the inner car. A microendoscope with a total outer diameter of 1.2 mm was developed in particular for easy visualization and of drug delivery to the RW niche. It incorporated a thin fiber optic, a working/laser channel (0.3 mm) and an irrigation/suction channel (0.27 mm). When compared to a common 30 degree lens optic, with the microendoscope a greater area of the round window niche could be overseen. In addition, the endoscope could be advanced directly upon the surface of the RW membrane (RWM). The microendoscope may be used for evaluation of the anatomy of the RW niche prior to the placement of local drug delivery systems, for application of drugs directly onto the surface of the RWM or to verify the correct placement of inner ear drug delivery systems.

L11 ANSWER 3 OF 17 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002137487 EMBASE
TITLE: [Gene therapeutic aspects of the ear].
GENTHRERAPEUTISCHE ASPEKTE AM INNENOHR.

AUTHOR: Pfister M.; **Lowenheim H**.
CORPORATE SOURCE: Dr. M. Pfister, Universitats-Hals-Nasen-Ohren-Klinik, Elfriede-Auihorn-Strasse 5, 72076 Tubingen, Germany. mpfister@hgmp.mrc.ac.uk
SOURCE: Medizinische Genetik, (2002) 14/1 (53-57).
Refs: 37
ISSN: 0936-5931 CODEN: MGENEZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 011 Otorhinolaryngology
022 Human Genetics
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: English; German

AB Hearing impairment is the most frequent sensory deficit and one of the most frequent chronic diseases of mankind. In Germany alone 16 million are affected by hearing impairment. Approximately 80% of these have sensorineural hearing loss which is caused by genetic, the aging process or exogenous influences. Usually this functional deficit is characterized by the irreversible loss of cellular elements in particular the sensory cells. At present the only available therapeutic option is symptomatic in the form of hearing aids. A causal therapeutic option for sensorineural hearing loss is not yet available. However, there is increasing understanding of the molecular basis of both genetic and acquired causes of this form of hearing impairment. From this progress in research certain target molecules can be derived. The identification of such drug targets could lead to the development of therapeutic concepts at the molecular level. The inner ear is an almost isolated liquid space and offers particular advantages for the local application of potential therapeutics. A specific therapeutic modality directly applicable to the inner ear has yet to be developed.

L11 ANSWER 4 OF 17 MEDLINE
ACCESSION NUMBER: 2002230072 IN-PROCESS
DOCUMENT NUMBER: 21964569 PubMed ID: 11967779
TITLE: [In Process Citation].
Grundlagen der In-vivo-Regeneration im Kopf-Hals-Bereich.
AUTHOR: **Lowenheim H**
CORPORATE SOURCE: Universitats-Hals-Nasen-Ohren-Klinik, Tubingen..
hubert.loewenheim@uni-tuebingen.de
SOURCE: LARYNGO- RHINO- OTOLOGIE, (2002 May) Suppl 1 1-23.
Journal code: 8912371. ISSN: 0935-8943.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020423
Last Updated on STN: 20020423

L11 ANSWER 5 OF 17 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001537266 MEDLINE
DOCUMENT NUMBER: 21228361 PubMed ID: 11330919
TITLE: The I' potential of the human auditory brainstem response to paired click stimuli.
AUTHOR: Davis-Gunter M J; **Lowenheim H**; Gopal K V; Moore E J
CORPORATE SOURCE: Department of Audiology and Speech Sciences, Michigan State University, East Lansing, USA.
SOURCE: SCANDINAVIAN AUDIOLOGY, (2001) 30 (1) 50-60.
Journal code: 0342230. ISSN: 0105-0397.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011008
Last Updated on STN: 20011008
Entered Medline: 20011004

AB When stimulated with an appropriate stimulus, the hair cells of the organ of Corti depolarize, causing the release of a neurotransmitter substance, which excites afferent VIIIth nerve dendrites. It is reasonable to hypothesize that excitatory postsynaptic potentials (EPSPs) generated by the dendrites of the auditory nerve in turn initiate a compound action potential (CAP). The EPSP is thought to be the generator potential for the CAP, and may be recorded in auditory brainstem responses (ABRs) as the I' potential. Determining the anatomical origin of I' may enhance the sensitivity of the ABR technique in hair cell/dendrite/auditory nerve evaluations. Whether I' is of sensory or of neural origin is equivocal, and therefore I' is not well understood. To investigate this dilemma, ABRs were recorded from human subjects using standard and paired-click stimuli, and using subtraction methods to generate a derived ABR. Two early peaks, designated as I degree and I', occurred before wave I in the derived ABR. It was hypothesized that peaks I degrees and I' represent the summating potential and the generator potential, generated by the cochlea and VIIIth nerve dendrites, respectively.

L11 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:662076 CAPLUS
TITLE: Methods for culturing fluid-filled sensory organs
INVENTOR(S): Kil, Jonathan; **Lowenheim, Hubert**; Sudra, Anish H.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000054583	A1	20000921	WO 2000-US5736	20000303
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1161142	A1	20011212	EP 2000-914825	20000303
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1999-123100P P 19990305
WO 2000-US5736 W 20000303

AB The present invention provides methods for culturing fluid-filled sensory organs in vitro . In particular, the present invention provides methods for culturing the eyeball, including the retina, and the inner ear, including the Organ of Corti, in vitro . The methods of the present invention involve little or no microsurgical dissection of the entire fluid-filled sensory organ, thereby preserving the structural and functional integrity of the sensory epithelium. The methods of the present invention include the steps of (a) introducing a fluid-filled

sensory organ (such as an inner ear or an eye ball) into a culture chamber
containing liquid culture medium and (b) moving the culture chamber so that the fluid-filled sensory organ moves within the culture chamber. Preferably the culture chamber is cylindrical or annular in shape and is rotated about its longitudinal axis.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 17 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999199314 MEDLINE
DOCUMENT NUMBER: 99199314 PubMed ID: 10097167
TITLE: Gene disruption of p27(Kip1) allows cell proliferation in the postnatal and adult organ of corti.
AUTHOR: **Lowenheim H**; Furness D N; Kil J; Zinn C; Gultig K; Fero M L; Frost D; Gummer A W; Roberts J M; Rubel E W; Hackney C M; Zenner H P
CORPORATE SOURCE: Department of Otolaryngology, University of Tubingen, Silcherstrasse 5, 72076 Tubingen, Germany.. hubert.loewenheim@uni-tuebingen.de
CONTRACT NUMBER: DC00247 (NIDCD)
DC02854 (NIDCD)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Mar 30) 96 (7) 4084-8. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990512
AB Hearing loss is most often the result of hair-cell degeneration due to genetic abnormalities or ototoxic and traumatic insults. In the postembryonic and adult mammalian auditory sensory epithelium, the organ of Corti, no hair-cell regeneration has ever been observed. However, nonmammalian hair-cell epithelia are capable of regenerating sensory hair cells as a consequence of nonsensory supporting-cell proliferation. The supporting cells of the organ of Corti are highly specialized, terminally differentiated cell types that apparently are incapable of proliferation. At the molecular level terminally differentiated cells have been shown to express high levels of cell-cycle inhibitors, in particular, cyclin-dependent kinase inhibitors [Parker, S. B., et al. (1995) Science 267, 1024-1027], which are thought to be responsible for preventing these cells from reentering the cell cycle. Here we report that the cyclin-dependent kinase inhibitor p27(Kip1) is selectively expressed in the supporting-cell population of the organ of Corti. Effects of p27(Kip1)-gene disruption include ongoing cell proliferation in postnatal and adult mouse organ of Corti at time points well after mitosis normally has ceased during embryonic development. This suggests that release from p27(Kip1)-induced cell-cycle arrest is sufficient to allow supporting-cell
proliferation to occur. This finding may provide an important pathway for inducing hair-cell regeneration in the mammalian hearing organ.

L11 ANSWER 8 OF 17 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999128011 MEDLINE
DOCUMENT NUMBER: 99128011 PubMed ID: 9930821
TITLE: Inverted papilloma of the nasal cavity and the paranasal sinuses: using CT for primary diagnosis and follow-up.
AUTHOR: Dammann F; Pereira P; Laniado M; Plinkert P; **Lowenheim H**; Claussen C D
CORPORATE SOURCE: Department of Diagnostic Imaging, University of Tuebingen, Germany.

SOURCE: AJR. AMERICAN JOURNAL OF ROENTGENOLOGY, (1999 Feb) 172 (2) 543-8.
Journal code: 7708173. ISSN: 0361-803X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990301
Last Updated on STN: 19990301
Entered Medline: 19990218

AB OBJECTIVE: Morphologic criteria for the diagnosis of primary and recurrent inverted papilloma as revealed on CT were evaluated in a large series. MATERIALS AND METHODS: Findings of 121 CT examinations that had been performed in 32 patients with histologically proven inverted papilloma were retrospectively analyzed using the following morphologic criteria: localization, size, surface configuration, and bony changes. RESULTS: Unilateral tumor localization involving the lateral nasal wall and the middle meatus was the feature that best correlated with the finding of primary inverted papilloma. A lobulated surface pattern was another typical sign, which was revealed on 19 of the 29 CT scans of patients with primary inverted papilloma. Although tumor localization and the finding of a newly grown soft-tissue mass were less reliable criteria to differentiate between recurrent inverted papilloma and postoperative complications or concomitant inflammatory disease, a lobulated surface pattern was seen on 26 of the 28 CT scans of patients with tumor recurrence but on only three of the 64 follow-up CT scans of patients without recurrent inverted papilloma. CONCLUSION: A unilateral mass within the nasal cavity or paranasal sinuses with a surface configuration that appears lobulated on CT is, to our knowledge, a new sign that strongly suggests inverted papilloma as a primary diagnosis and also suggests inverted papilloma in patients with tumor recurrence.

L11 ANSWER 9 OF 17 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999180316 MEDLINE
DOCUMENT NUMBER: 99180316 PubMed ID: 10082279
TITLE: Determination of hair cell degeneration and hair cell death in neomycin treated cultures of the neonatal rat cochlea.
AUTHOR: **Lowenheim H**; Kil J; Gultig K; Zenner H P
CORPORATE SOURCE: Department of Otorhinolaryngology, University of Tubingen, Germany.. hubert.loewenheim@uni-tuebingen.de
SOURCE: HEARING RESEARCH, (1999 Feb) 128 (1-2) 16-26.
Journal code: 7900445. ISSN: 0378-5955.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990427

AB The spatial-temporal course of hair cell degeneration and hair cell death was examined in the mammalian cochlea following aminoglycoside treatment. Organotypic cultures were established from postnatal rats (P3) and treated with 1 mM neomycin sulfate for 12-48 h and analyzed using a live/dead assay under epifluorescence microscopy. Live hair cells were labeled with calcein, a probe whose fluorescence and cellular retention depends upon intracellular esterase activity and cell-membrane integrity, respectively.
Hair cell death was determined by ethidium homodimer-1, a probe that can

enter cells with compromised cell membranes only. Inside the cell it binds to DNA. Hair cell morphology was also examined using phalloidin labeling, scanning electron microscopy and semi-thin section analysis. Results showed that hair cell degeneration and hair cell death occurred in a time dependent gradient from base to apex. After 48 h of neomycin treatment, most apical hair cells survived while most basal hair cells died. Calcein labeling provides a sensitive functional assay for measuring hair cell survival.

L11 ANSWER 10 OF 17 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1998034327 MEDLINE
DOCUMENT NUMBER: 98034327 PubMed ID: 9369394
TITLE: Trends and perspectives in minimally invasive surgery in otorhinolaryngology-head and neck surgery.
AUTHOR: Plinkert P; **Lowenheim H**
CORPORATE SOURCE: Department of Otorhinolaryngology, University of Tubingen, Germany.
SOURCE: LARYNGOSCOPE, (1997 Nov) 107 (11 Pt 1) 1483-9. Ref: 17
Journal code: 8607378. ISSN: 0023-852X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 20000303
Entered Medline: 19971216

AB The roots of minimally invasive surgery (MIS) in otolaryngology-head and neck surgery (ORL-HNS) can be traced to the 1950s. Today, endonasal sinus surgery and endolaryngeal surgery already fulfill the principles of MIS. To widen its spectrum of indications, however, MIS must be able to offer three advantages that conventional macrosurgery and microsurgery already have: free maneuverability for the instrument, sensory feedback, and three-dimensional imaging. Every anatomical region (e.g., paranasal sinuses, upper aerodigestive tract, cerebellopontine angle) requires specific surgical instrumentation. Here, the authors present recently developed steerable instruments that allow two additional degrees of freedom not attainable with conventional instruments. These instruments may permit access to problem zones (e.g., laterally extending frontal and ethmoidal sinus recesses) in the near future. For better control of the instrument and the operative procedure, tactile feedback can be achieved with appropriate microsensor systems. Three-dimensional vision can be realized by three-dimensional video-endoscopes and sequential image processing.

L11 ANSWER 11 OF 17 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97455228 MEDLINE
DOCUMENT NUMBER: 97455228 PubMed ID: 9376035
TITLE: [Bilateral vestibular loss as a post-infection complication of yersiniosis?].
Bilateraler Vestibularisausfall als postinfektiose Komplikation einer Yersiniose?.
AUTHOR: Bucheler M; **Lowenheim H**
CORPORATE SOURCE: Universitat Leipzig, Klinik und Poliklinik fur Hals-, Nasen-, Ohrenheilkunde, Leipzig.
SOURCE: LARYNGO- RHINO- OTOLOGIE, (1997 Aug) 76 (8) 502-5.
Journal code: 8912371. ISSN: 0935-8943.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711

ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971120

AB BACKGROUND: Yersinia infections other than plaque are caused by Yersinia pseudotuberculosis and Yersinia enterocolitica. Food and water contamination as well as animal-to-person and person-to-person contact are common pathways of transmission. Clinical manifestations include enteritis, enterocolitis, acute appendicitis, inflammation of the terminal ileum, and mesenteric adenitis. Y. enterocolitica may cause bacteremia with subsequent septicemia predominantly in patients with underlying illnesses such as diabetes mellitus or malignancy. More frequently enteritis is followed by immunological post-infectious syndromes such as arthritis and erythema nodosum. The present case report discusses bilateral vestibular loss possibly caused by an infection with Y. enterocolitica. PATIENTS: A 27-year-old caucasian woman initially presented with the otologic symptom of spinning vertigo accompanied by nausea and vomiting. RESULTS: Physical exam revealed spontaneous nystagmus to the left. Bithermal caloric responses were absent. Pure tone audiometry showed a bilateral symmetric high-frequency sensorineural hearing loss. Neurologic exams did not reveal involvement of the central vestibular system. Perilymphatic fistula on the left side was excluded by tympanoscopy. Serology for rheumatoid factors and HLA B27 was negative. Lead or mercury intoxication was also excluded. In her medical history the patient reported intermittent watery diarrhea and stress dependent arthralgia that had commenced during a stay in Argentina three years ago. Serology was positive, revealing elevated titers for Y. enterocolitica type 3 (1:200) and type 9 (1:400). DISCUSSION: Bilateral vestibular loss is rare. The main cause is aminoglycoside ototoxicity or meningitis. Yersina infections have not yet been described as inducing disease of the labyrinth. Present pathophysiologic knowledge of yersinia infections is described as follows: After peroral infection, gastrointestinal permeability is increased. Low-molecular-weight substances may enter the bloodstream and stimulate the formation of circulating immune complexes. These are held responsible for extraintestinal manifestations of yersinosis. Whether these circulating immune complexes and antibodies against Y. enterocolitica have an effect on the inner ear remains unclear.
CONCLUSION: Because the coincidence of yersiniosis and a bilateral vestibular loss with no other identified cause, a postinfectious immune response is suggested as possible pathogenic mechanism.

L11 ANSWER 12 OF 17 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 97295525 MEDLINE
DOCUMENT NUMBER: 97295525 PubMed ID: 9221255
TITLE: [Molecular biology in oncology of head-neck tumors]. Molekularbiologie in der Onkologie von Kopf-Hals-Tumoren.
AUTHOR: **Lowenheim H**
CORPORATE SOURCE: Universitats-HNO-Klinik Tubingen.
SOURCE: HNO, (1997 Apr) 45 (4) 185-6.
Journal code: 2985099R. ISSN: 0017-6192.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Conference; Conference Article; (CONGRESSES)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970724
Last Updated on STN: 19990129
Entered Medline: 19970714

L11 ANSWER 13 OF 17 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 95332038 MEDLINE

DOCUMENT NUMBER: 95332038 PubMed ID: 7607908
TITLE: [Hair cell regeneration in the inner ear of birds and mammals].
Haarzellregeneration im Innenohr bei Vogeln und Saugern.
AUTHOR: **Lowenheim H**
CORPORATE SOURCE: Universitats-HNO-Klinik Tubingen.
SOURCE: HNO, (1995 May) 43 (5) 269-70.
Journal code: 2985099R. ISSN: 0017-6192.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950828
Last Updated on STN: 19950828
Entered Medline: 19950811

L11 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1927:16476 CAPLUS
DOCUMENT NUMBER: 21:16476
ORIGINAL REFERENCE NO.: 21:2046h-i
TITLE: Indian tea fungus (Teepilz)
AUTHOR(S): **Lowenheim, H.**
SOURCE: Apoth. Ztg. (1927), 42, 148-9
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB An examn. has been made of the beverage resulting from the fermentation of an aq. soln. of sugar ext. of black tea induced by a tea fungus (Teepilz).
In its younger stages it has a pleasant sweet-acid taste, contg. among other ingredients CO2, AcOH, lactic acid and EtOH. If the fermentation proceeds for a period of 10 to 15 days, the liquid becomes strongly acid, the taste astringent and producing if drunk serious gastronomic disturbances.

L11 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1925:5832 CAPLUS
DOCUMENT NUMBER: 19:5832
ORIGINAL REFERENCE NO.: 19:801e-h
TITLE: The qualitative and quantitative analysis of sodium dithionate
AUTHOR(S): Litterscheid, F. M.; **Lowenheim, H.**
SOURCE: Chem.-Ztg. (1924), 48, 881-3
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Crystals of com. Na2S2O6 possess varying amts. of H2O of hydration. Qual tests should preceed a quant. analysis of the salt. Heat gradually about 1 g. of the salt in a long glass combustion tube to dull redness. Only H2O should be evolved at first and at higher temps. only SO2. A brown sublimate of S or a blackening of the salt indicates impurities. Five cc. portions of a soln. of 3 g. of the salt in 30 cc. of H2O should be tested qualitatively for SO4-, Cl-, SO3-, CO3-, Ca++, Ba++, Mg++, Cu++, Fe++ and Fe+++. In the qual. analysis, weigh 0.25-0.35 g. of the finely ground salt into a porcelain or Pt boat and dry at 60.degree. for 1 1/2 hr., then at 100.degree. for 1/2 hr. Det. the H2O from the loss in wt. Place the boat in a 50 cm. combustion tube and insert in a combustion furnace with about 10 cc. of each end of the tube projecting. Displace the air in the tube with dry CO2 and heat to dull redness. Sweep out the evolved SO2 by means of a slow current of CO2 into an absorption tube contg. 50 cc. of 0.1 N I soln. Weigh the residue of Na2SO4 and titrate the excess I soln. to det. the SO2. If desired, the H2O may be detd. from the increase in wt. of a CaCl2 drying tube placed between the combustion tube and the I absorption tube. The analysis may. also be made by detg. the H2O from the

loss in wt. at 60-100.degree. as above, and the SO2 from the loss in wt. at 250.degree..

L11 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1921:13067 CAPLUS
DOCUMENT NUMBER: 15:13067
ORIGINAL REFERENCE NO.: 15:2442b-i,2443a
TITLE: Two new reduction products of codeine
AUTHOR(S): Mannich, C.; **Lowenheim, H.**
SOURCE: Arch. Pharm. (1920), 258, 295-316
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
GI For diagram(s), see printed CA Issue.
AB The difficulties encountered in the investigation of morphine and codeine, due to rearrangement into apomorphine, migration of the OH group (Knorr, C. A. 11, 1285), or the elimination of C atoms, along with N, by exhaustive methylation, are all connected with the partly reduced benzene nucleus. The authors have, therefore, sought a means of so modifying this nucleus by well defined processes as to obviate the occurrence of the anomalous behavior referred to, and so permit the application of the usual methods for detg. constitution. Dihydrocodeine (Skita and Frank, C. A. 6, 231) may be obtained in 3 forms; a dihydrate, C18H23O3N.2H2O, which seps. from alc. in large plates, m. 55.degree., and is converted above its m. p. into a 2nd dihydrate, m. 87-8.degree.; the anhydrous compd. m. 111-2.degree.. It is unchanged by distn. with CH2O2, but with HI gives dihydromorphine, m. 156-8.degree.. Chlorodihydrocodide (Freund, C. A. 15, 834), m. 172-4.degree., gives a hydrochloride, m. 203.degree., and a methiodide, C19H25O2NClI, needles, m. 244.degree., and is converted by HI into chlorodihydromorphide, C17H20O2NCl, prisms, m. 233.degree., which is apparently dimorphous. The Cl atom in these compds. is very inert, and could not be replaced by H. Freund's results from the reduction of .alpha.-chlorocodide were confirmed, but, in addition, small quantities of the products of reduction of .beta.-chlorocodide were observed. The latter compd., in presence of Pd, gave rise to a mixt. in which deoxydihydrocodeine, C18H23O2N, m. 107.degree., [.alpha.]D -81.47.degree., predominated. It contains 1 MeO group, and gives a yellow picrate, m. 207.degree., but no Ac deriv. In it, therefore, the object of the investigation as above described, is attained, since the OH group of codeine is replaced by H, and the benzene nucleus in question reduced. Correspondingly, its methiodide, C19H26O2NI, prisms, m. 256-7.degree., behaves normally towards KOH, and gives deoxydihydrocodomethine, C19H25O2N, m. 86.degree. (picrate m. 154.degree.; hydrochloride, C19H25O2N.HCl.H2O, needles, m. 222.degree.). From its methiodide, C20H28O2NI, needles, m. 238.degree., by treatment with KOH, Me3N and 3-methoxy-5-vinylhexahydrophenanthrylene oxide (annexed formula) C17H18O2, prisms, m. 80.degree., were obtained. The latter compd. gives an oily dibromide, and, by reduction in the presence of Pd, 3-methoxy-5-ethylhexahydrophenanthrylene oxide, prisms, m. 69.degree.. Deoxytetrahydrocodeine, C18H25ON2.0.5H2O, needles, m. 144-5.degree., [.alpha.]D-36.92.degree., is the 2nd product of reduction of .beta.-chlorocodide, and is also obtained by Clemmensen's method from dihydrocodeinone, C18H21O3N, m. 193-4.degree. (hydro chloride, C18H21O3N.HCl.2H2O, m. 82.degree.; oxime, C18H22O3N2, m. 266.degree.), which is itself obtained from codeinone by reduction in the presence of Pd. Deoxytetrahydrocodeine gives a methiodide, C19H28O2NI, needles, m. 256.degree., but no Ac nor Bz deriv.

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